

# EUROPEAN WORKSHOP

## Current Insights into Group B Streptococcal Diseases

### Programme & Abstracts Book

Golden Bay Beach Hotel,  
Larnaca, Cyprus  
27- 28 May 2009



# Acknowledgements

We would like to thank the following for the support that they have provided towards this workshop:

Golden Bay Beach Hotel, Larnaca, Cyprus  
Archbishop Makarios III Hospital, Nicosia, Cyprus  
GATC Biotech, Konstanz, Germany  
Cepheid Europe, Maurens-Scopont, France

## Scientific Committee

Dr John Telford (Italy)  
Dr Graziella Orefici (Italy)  
Dr Androulla Efstratiou (UK)  
Dr Baharak Afshar (UK)  
Dr Pierrette Melin (Belgium)  
Prof Mogens Kilian (Denmark)  
Dr Manuel de la Rosa Fraile (Spain)  
Dr Maria Koliou (Cyprus)  
Dr Andreas Hadjidemitriou (Cyprus)

## Organising Committee

Miss Sophia Masud (UK)  
Dr Antonella Chiucchiuini (Italy)  
Miss Laura Giordano (Italy)

**\* Our thanks to all speakers and chairpersons for their contributions.**

# Introduction

## Dear Participants

On behalf of the Scientific and Organising Committee we would like to extend our very warm personal greetings to you all. It is our pleasure to welcome you to the first European Workshop on 'Current Insights into Group B Streptococcal Diseases' on the beautiful island of Cyprus.

We welcome participants from 15 different countries including EU member states in addition to Israel and the USA. This Workshop is part of the dissemination and training activities of the DEVANI (DEsign of a Vaccine Against Neonatal Infections) project, launched on 1 January 2008. The DEVANI project is a three year pan-European programme funded through the European Commission Seventh Framework and is coordinated by Novartis Vaccines & Diagnostics, Siena, Italy. The overall objective of the study is to design a vaccine to immunize neonates against group B streptococcus (GBS) infections through a durable maternal immune response.

The Workshop is co-organized by the Health Protection Agency Centre for Infections (London, UK) and ALTA (Siena, Italy). The purpose of this Workshop is to provide European students, laboratory researchers, scientists, clinicians and public health specialists with the latest updates in the field of GBS diseases. During this workshop we will have the opportunity to discuss microbiological, epidemiological and clinical aspects of GBS diseases as well as the recent developments in the field of GBS vaccines.

We wish you all a successful and fruitful conference and an equally enjoyable stay in the beautiful Eastern Mediterranean on the island of Aphrodite! Savour the extraordinary loveliness of this island and enjoy the Greek Cypriot hospitality.

## Welcome to Cyprus!

**Androulla Efstratiou & Baharak Afshar**  
On behalf of the Scientific & Organising Committee



# Chairpersons

**Dr Baharak Afshar**

Health Protection Agency Centre for Infections, London, UK

**Prof Reinhard Berner**

University Children's Hospital, Freiburg, Germany

**Dr Manuel De La Rosa Fraile**

Hospital Universitario Virgen de las Nieves, Granada, Spain

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**Prof Carol Baker**

Baylor College of Medicine, Houston, Texas, USA

**Dr Alberto Berardi**

Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy

**Prof Monica Farley**

Emory University School of Medicine, Atlanta, Georgia, USA

**Dr Philippe Glaser**

Pasteur Institute, Paris, France

**Dr Andreas Hadjidemitriou**

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**Prof Claire Poyart**

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**Prof Barbara Spellerberg**

University of Ulm, Ulm, Germany

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**Dr Levantia Zachariadou**

Aghia Sophia" Children's Hospital, Athens, Greece



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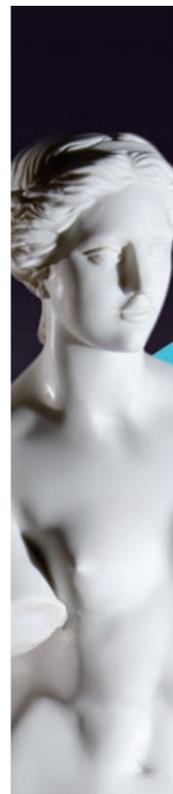
## United Kingdom

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**Dr Phil Ward**

Universities of Nottingham &amp; Oxford, UK

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Baylor College of Medicine, Houston, Texas, USA

**Prof Monica Farley**

Emory University School of Medicine, Atlanta, Georgia, USA

# Programme

## EUROPEAN WORKSHOP

### Current Insights into Group B Streptococcal Diseases

## Day 1: Wednesday 27 May 2009

08.10 - 09.10

**Registration**

09.10 - 09.30

**Opening address****Dr Androulla Agrotou** (Director of Medical and Public Health Services, Cyprus Ministry of Health, Nicosia - Cyprus)**Dr Andreas Hadjidemitriou** (Director, Paediatrics Department, Archbishop Makarios III Hospital, Nicosia - Cyprus)

## Session 1

**Chairs:**

Dr Androulla Efstratiou (Health Protection Agency Centre for Infections, London - UK)

Dr Graziella Orefici (Istituto Superiore di Sanità, Rome - Italy)

09.30 - 10.30

**Key Opening Lecture****GBS Overview: Victories and Vexations***Prof Carol Baker* (Baylor College of Medicine, Houston, Texas - USA) (Abs. 1. 1)

10.30 - 11.15

**Epidemiology of GBS and Screening Strategies***Prof Monica Farley* (Emory University School of Medicine, Atlanta, Georgia - USA) (Abs. 1.2)

11.15 - 11.45

**Coffee**

11.45 - 12.15

**Pathogenesis of GBS***Prof Barbara Spellerberg* (University of Ulm, Ulm - Germany) (Abs.1.3)

12.15 - 12.45

**Clinical management of GBS diseases: a paediatrician's perspective***Dr Maria Koliou* (Archbishop Makarios III Hospital, Nicosia Cyprus) (Abs. 1.4)

12.45 - 14.00

**Lunch**

## Day 2: Thursday 28 May 2009

### Session 2

#### Chairs:

Dr Manuel De La Rosa Fraile (Hospital Universitario Virgen de las Nieves, Granada Spain) Dr Paula Krizova (National Institute of Public Health, Prague Czech Republic)

- 14.00 - 14.30      **GBS invasive disease: a two-year survey by the French National Reference Centre for Streptococci**  
*Prof Claire Poyart (Université Paris Descartes, Paris - France) (Abs. 2.1)*
- 14.30 - 15.00      **Early onset group B streptococcus infections in Emilia-Romagna, Italy**  
*Dr Alberto Berardi (Azienda Ospedaliero Universitaria Policlinico, Modena - Italy) (Abs. 2.2)*
- 15.00 - 15.30      **Tea**
- 15.30 - 16.00      ***Streptococcus agalactiae* infections in Greece: an overview**  
*Dr Levantia Zachariadou ("Aghia Sophia" Children's Hospital, Athens - Greece) (Abs. 2.3)*
- 16.00 - 16.30      **Changing epidemiology of invasive GBS disease in England and Wales**  
*Dr Theresa Lamagni (Health Protection Agency Centre for Infections, London - UK) (Abs. 2.4)*
- 16.30 - 17.30      **Poster viewing**
- 17.30              **End of day one**



### Session 3

#### Chairs:

Prof Mogens Kilian (Aarhus University, Aarhus - Denmark).  
Prof Reinhard Berner (University Children's Hospital, Freiburg - Germany)

- 09.30 - 10.00      **Overview of DEVANI**  
*Dr Graziella Orefici (Istituto Superiore di Sanità, Rome - Italy) (Abs. 3.1)*
- 10.00 - 10.30      **GBS vaccine developments**  
*Dr John Telford (Novartis Vaccines and Diagnostics, Siena - Italy) (Abs. 3.2)*
- 10.30 - 11.00      **Coffee**
- 11.00 - 11.30      **GBS: screening, diagnosis and clinically relevant antimicrobial resistance**  
*Dr Pierrette Melin (CHU and ULg, Liege - Belgium) (Abs. 3.3)*
- 11.30 - 12.00      **Overview of GBS molecular typing methods**  
*Dr Knud Poulsen (Institute of Medical Microbiology and Immunology, Aarhus - Denmark) (Abs. 3.4)*
- 12.00 - 13.30      **Lunch**

### Session 4

#### Chairs:

Dr Baharak Afshar (Health Protection Agency Centre for Infections, London - UK)  
Dr Antoaneta Detcheva (National Center of Infectious and Parasitic Diseases, Sofia - Bulgaria)

- 13.30 - 14.00      ***Streptococcus agalactiae* genomics and proteomics**  
*Dr Philippe Glaser (Institut Pasteur, Paris - France) (Abs. 4.1)*
- 14.00 - 14.30      **General discussion and closing remarks**  
*Dr Graziella Orefici (Istituto Superiore di Sanità, Rome - Italy)*
- 14.30 - 16.00      **Tea and poster session**
- 16.00              **End of workshop**



# Biographies of Chairperson and Speakers



**Dr Baharak Afshar** completed her first degree, in Biotechnology, at the King's College London (KCL) University in London, in 1997. She was awarded a PhD on 'Diversity of *Mycoplasma fermentans*' at KCL University, in 2002. Whilst writing up her PhD thesis, Baharak worked for a year as a Forensic Scientist at the Forensic Science Service in London. In 2002, she was appointed to the post of Legionella Project Scientist within the Atypical Pneumonia Unit, Respiratory and Systemic Infections Department (RSID), Health Protection Agency Centre for Infections (HPACfI). During this post, Baharak was involved in developing and evaluating various molecular methods for the epidemiological typing of *Legionella pneumophila* strains. She also managed a number of multi-centre external quality assessment (EQA) schemes for the detection, identification and

molecular typing of *L. pneumophila*. In April 2008, Baharak joined the Streptococcus and Diphtheria Reference Unit, RSID, HPACfI as a DEVANI Project Scientist, funded through the European Commission Seventh Framework. Baharak is currently involved with a number of work packages within this pan-European programme.

**Dr Androulla Agrotou** has been the director of the Medical and Public Health Services at the Ministry of Health in Nicosia, Cyprus, since 2007. She was acting director of the Medical and Public Health Services from 2004 to 2007 and the Chief Medical Officer from 1995 to 2004. Dr Agrotou obtained her diploma in medicine at the Moscow Medical School, Russia, in 1971, and her registration as a Medical Practitioner from the Cyprus Medical and Dental Council in 1972. Dr Agrotou completed her Master in Public Health (MPH), at Dundee University in Scotland in 1989, before obtaining her Specialisation in Public Health and Community Medicine from the Cyprus Medical and Dental Council in 1990. A year later, she was awarded a MBA, at the Mediterranean Institute of Management. In 2003, she completed her Specialisation in General Medicine from Cyprus Medical and Dental Council. Dr Agrotou has participated, coordinated and presented at medical and scientific conferences, seminars and workshops both locally and internationally.



**Prof Carol Baker** is professor of paediatrics and of molecular virology and microbiology at Baylor College of Medicine in Houston, Texas. She also is the Texas Children's Hospital Foundation Chair in Paediatric Infectious Diseases. Dr Baker serves as Past President of the National Foundation for Infectious Diseases and is Vice-Chair of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices. Previously, she has been Secretary of the Paediatric Infectious Diseases Society, President of the Infectious Diseases Society of America and a member of the American Academy of Paediatrics Committee on Infectious Diseases. Dr Baker's work has focused on all aspects of paediatric infectious diseases, particularly all aspects of group B streptococcal infections including research to develop a

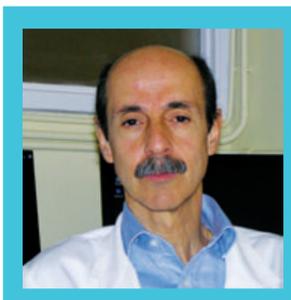
vaccine. Her work policy in the early 1990s led to the U.S. recommendations for intrapartum chemoprophylaxis to prevent early-onset group B streptococcal disease in neonates. In 1997, Dr Baker was the recipient of the Distinguished Service Award and in 2007 of the Distinguished Physician Award, each from the Paediatric Infectious Diseases Society. In 2008 she received the Distinguished Alumna Award from Baylor College of Medicine and the Mentor Award from the Infectious Diseases Society of America. A widely published researcher in paediatrics and infectious diseases, Dr Baker has authored or co-authored more than 300 original articles, reviews and book chapters. She is an associate editor of the 2000, 2003, 2006 and 2009 Red Book published by the

American Academy of Paediatrics and an editor of Infectious Diseases of the Fetus and Newborn Infant (6th edition). Dr Baker received her medical degree, completed her residency and held fellowships in the department of paediatrics, infectious disease section at Baylor College of Medicine. She was a research fellow in medicine at Harvard Medical School and a clinical fellow in medicine at Boston City Hospital in Boston, Massachusetts. Dr Baker received her undergraduate degree from the University of Southern California in Los Angeles, California.

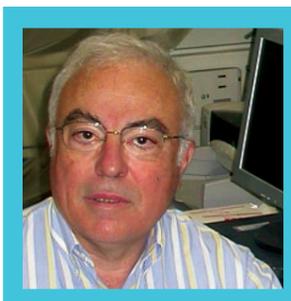


**Prof Reinhard Berner** has trained in Clinical Microbiology, Paediatrics (Board Certificate 1997), Paediatric Infectious Diseases (Board Certificate 2000), Infectious Diseases (Board Certificate 2006), and Paediatric Rheumatology (Board Certificate 2007). He has been the Vice-Chairman for Centre for Paediatrics and Adolescent Medicine, University Medical Centre Freiburg, Germany, since 2003 and the Chairman for the Division of Paediatric Infectious Diseases, Immunology and Vaccinology, University Medical Centre Freiburg, since 2006. In 2005 he was appointed as the President German Society for Paediatric Infectious Diseases (DGPI) and became a Board Member for the Chronic Immunodeficiency Centre, University Medical Centre Freiburg in 2008.

Prof Berner's main research interests include: Neonatal immune response to group B streptococcus (GBS), Clinical and molecular epidemiology of GBS, Clinical and molecular epidemiology of respiratory tract pathogens (viral and bacterial) in children as well as Clinical trials in children with particular interest in anti-infectives and vaccines.



**Dr Alberto Berardi** is a staff physician at the Neonatal Intensive Care Unit, Paediatrics Departments, Policlinico Hospital in Modena, Italy. Dr Berardi completed his MD in Medicine and Surgery in 1983 at the University of Modena, Modena, Italy. In 1987, he obtained his Specialisation degree in Paediatrics at the same university. In 1990, he was awarded a Specialist degree in Allergology at the University of Parma, Parma, Italy before completing his post-graduation in Neonatology at the University of Modena in 1992. Dr Berardi is the leader of the GBS Prevention Working Group which was set up in Emilia-Romagna, an Italian region, in 2001. This group involves a network of neonatologists, paediatricians and microbiologists. They have implemented prevention strategies and have obtained the first Italian area-based data on GBS disease, a prevention model used throughout the country.



**Dr Manuel De La Rosa Fraile** is the former Chief of Service of Microbiology at the Virgen de las Nieves University Hospital in Granada, Spain (1979 -2008). He is also the director of the research group in Microbiology at Virgen de las Nieves Hospital. He has been involved in GBS research since 1981 and since then he has published many studies on GBS diagnostic techniques. He has developed the Granada Medium and has identified the pigment of GBS as a polyene (granadaene). He is an adviser on GBS neonatal infection of the Spanish societies of Obstetrics & Gynecology, and Neonatology. In 2002 he chaired the First European Workshop on GBS Neonatal Disease Prevention in Granada (Spain). He is currently the Spanish coordinator for the DEVANI project and the director of the Cellular Production Unit at the University Hospital Virgen de las Nieves.



**Dr Antoaneta Detcheva** received her higher medical education at the Bulgarian Medical Academy in Sofia, (Bulgaria) in 1988 and her specialisation in Microbiology at the Higher Medical Institute, in 1993. She worked as a medical doctor at the Clinical Laboratory of the local hospital of Bobovdol town, Bulgaria from 1988 to 1989 before working as a research fellow in Microbiology at the National Centre for Infectious and Parasitic Diseases in 1989. She has been the head of the National Reference Laboratory for Streptococci and Corynebacteria at the National Centre of Infectious and Parasitic Diseases in Sofia, Bulgaria since 1994.



**Dr Androulla Efstratiou** was awarded a doctorate, PhD in medical microbiology by the University of London in 1987 and appointed to the post of Senior Microbiologist in 1989 at the then, Public Health Laboratory Service in London. In 1994, was appointed Head of the National Streptococcus Reference Laboratory and in June 1998 officially appointed as Head of the newly designated WHO Collaborating Centre for Reference and Research on Diphtheria and Streptococcal Infections. Dr Efstratiou is currently a Consultant Clinical Microbiologist within the Health Protection Agency Centre for Infections, Respiratory and Systemic Infections Department in London, UK, within which the WHO Collaborating Centre and National Reference Laboratory is situated. Present appointments also include; European Commission DG Research Evaluator, WHO Adviser/Consultant on diphtheria and streptococcal infections,

Project Leader of the European Diphtheria Surveillance Network (DIPNET), Consultant on streptococcal infections for the National Institutes of Health, Bethesda, Maryland, USA, UK Team leader for the European Commission DEVANI project and Coordinator of the International Committee on Group A Streptococcal Typing. Dr Efstratiou has more than 150 peer reviewed publications and more than 250 abstract presentations in the field of respiratory and systemic infections, notably streptococcal infections and those caused by *Corynebacterium diphtheriae* and *C.ulcerans*.



**Prof Monica Farley** has been a Professor of Medicine at the Department of Medicine, Emory University School of Medicine, Atlanta, USA since 1999. Her other current titles and affiliations include: Associate Professor of Microbiology and Immunology; Staff Physician at the VA Medical Centre in Atlanta; Director of the Georgia Emerging Infections Programme; Associate Director of the Division of Infectious Diseases at the Department of Medicine, Emory University School of Medicine. Professor Farley was also a member of the FDA Advisory Committee for vaccines and Related Biological Products between 2004 to 2007.



**Dr Philippe Glaser** earned his PhD from the University Pierre et Marie Curie (Paris, France) for studies on the Bordetella pertussis adenylate cyclase toxin, which he did in the laboratory of Antoine Danchin at the Institut Pasteur. He worked as a postdoctoral fellow in the laboratory of Jeff Errington at Oxford University, UK, where he examined the cellular localization of Spo0J protein in *Bacillus subtilis*. He returned to the Institut Pasteur, where he is studying the evolution and adaptation of human opportunistic pathogens, including *Streptococcus agalactiae*.



**Dr Andreas Hadjidemetriou** graduated in 1974 from the Medical school of the University of Athens, Greece. He received his specialization in the field of Paediatrics following his training at the A' University Paediatric Clinic of "Agia Sofia" Children's Hospital. He then obtained specialization in the field of Neonatology, having worked as a consultant in the Neonatal Intensive Care Unit of the A' University Paediatric Clinic of "Agia Sofia" Children's Hospital. In 1983, he completed his Doctorate at the University of Athens and joined the Medical Services of the Ministry of Health of the Republic of Cyprus and set up the Neonatal Intensive Care Unit at the Archbishop Makarios III Hospital in Nicosia, in 1985. He was granted a scholarship by the Council of Europe and pursued post-doctorate studies at the Neonatal Intensive Care Unit of the University

Hospital of King's College in London, in 1989; four years later he was promoted to the post of Director of the Neonatal Intensive Care Unit of Archbishop Makarios III Hospital in Nicosia. In 2008, he was appointed Director of the Paediatric Clinic of Archbishop Makarios III Hospital in Nicosia. Dr Hadjidemetriou is the founder member of the Hellenic Perinatal Society and is also the founder member and President of the Cyprus Perinatal Society.



**Prof Mogens Kilian** is professor of medical microbiology at the University of Aarhus (since 1991). He has a DDS degree from 1968 and a D. Sc. degree from 1975. He trained in clinical microbiology 1970-74 and was a visiting professor at the Department of Microbiology, University of Alabama at Birmingham, USA 1977-79, professor and chairman of Oral Biology, Royal Dental College, Aarhus, from 1981-91. Member of the editorial board of 5 international scientific journals including Infection and Immunity, Microbiology, and Journal of Clinical Microbiology, ad hoc referee for multiple periodicals in microbiology and immunology and for national research councils abroad. Member of the Danish Medical Research Council and its executive board 1988-91. Member of the Danish Committee for Scientific Dishonesty and the Senate of Aarhus University.

Organizer and co-organizer of 9 international scientific conferences in microbiology and immunology. Research in molecular microbial evolution, taxonomy, ecology and pathogenesis. Has published more than 200 scientific papers.



**Dr Maria Koliou** is a Paediatrician and Infectious Disease Specialist and currently works at the Paediatric Department of Archbishop Makarios III Hospital in Nicosia, Cyprus. She did her undergraduate studies at the Medical School of the University of Athens in Greece and specialised in paediatrics at the First Paediatric Clinic of the University of Athens at "Agia Sofia" Children's Hospital. Her PhD studies were on Neonatal Immunobiology at the same University. In 1999, she went to London where she specialised in infectious diseases and also did an MSc in Clinical Microbiology at the University of London. Since 1991, she has worked for the Government Health Services in Cyprus in several hospitals and has been at her current post at the Makarios Hospital since 1996. When she returned from her studies in London she founded the Infectious Diseases and Immunology Unit

and also the Infectious Disease Research Laboratory of Archbishop Makarios III Hospital. Dr Koliou is the Infection Control doctor for the Hospital and also Consultant in Infectious Diseases of the Oncology Center of the Bank of Cyprus. She teaches paediatric residents at her hospital and also nursing students at the Cyprus University of Technology Department of Nursing. Her research interests include the study of streptococci and also the epidemiology and immunological aspects of infection. She has also conducted research on zoonoses such as the rickettsial diseases, toxoplasmosis and leishmaniasis in Cyprus. Dr Koliou has participated in research projects funded by European and local funding organisations and collaborates with many well known research centres such as the Health Protection Agency, University Of Cyprus Department Of Biological Sciences, University of Athens and

the University of Crete. She has also been an invited speaker in various International and local Scientific conferences. For the last few years, she has served as a member in various National committees for the surveillance and control of infectious Diseases.



**Dr Paula Krizova** is head of the Airborne Bacterial Infections Department at the National Institute of Public Health in Prague, head of WHO Collaborating Centre for Reference and Research on Streptococci and also head of the National Reference Laboratory for Meningococcal Infections. She has worked as a WHO epidemiologist in the Smallpox Eradication Programme in India. She is the chief editor of *Epidemiology, Microbiology, Immunology* and member of the Editorial Board of *Central European Journal of Public Health*. She is a president of the Czech Society for Epidemiology and Microbiology and a member of the committee of the Czech Society for Vaccinology. She is a National Microbiology Focal Point in ECDC for the Czech Republic and has participated and currently

participates in EU projects: EU-MenNet, Strep-EURO, DEVANI, EU-IBIS and IBI. She has more than 350 publications under five variations of the name: P. Krizova, P. Kriz, P. Krizova-Kuzemenska, P. Kriz-Kuzemenska and P. Kuzemenska.



**Dr Theresa Lamagni** graduated in Psychology in 1994 and then worked in the voluntary-sector (drug misuse services) for a year. Theresa came to work for the Public Health Laboratory Service Communicable Disease Surveillance Centre in 1995, working on various HIV and STI surveillance programmes. During this time she also completed an MSc in Epidemiology at the London School of Hygiene & Tropical Medicine. In May 2001, she joined the newly formed Healthcare Associated Infection & Antimicrobial Resistance Department, now part of the Health Protection Agency Centre for Infections, as a senior epidemiologist. She is involved in a range of national and international projects concerned with developing new surveillance initiatives, research programmes and public health policies

relating to streptococcal, fungal and healthcare-associated infections. She completed her PhD on the epidemiology of severe group A streptococcal infections in Europe at the University of Helsinki in 2008.



**Dr Pierrette Melin** post-graduated as a pharmacist specialist in clinical biology from University of Liege, Belgium in 1982 and was awarded a PhD in Biomedical and Experimental Sciences from University of Liege, Belgium, for a research in "epidemiology of group B streptococci among pregnant women and infants" in 1987. Dr Melin is currently the Associate Head of the Department of Medical Microbiology at the University Hospital of Liege, the associate Professor of Microbiology at University of Liege and a director of the National Reference Centre for Group B Streptococci, in Belgium. Her research interests include group B streptococcal disease and prevention, Epidemiology, prevention strategies of perinatal infections, development and evaluation of rapid diagnostic methods, Cooperation in

GBS epidemiology with University of Leon, Nicaragua and University of Montevideo, Uruguay. Among alternative subjects of interest: antimicrobial resistance mechanisms.



**Dr Graziella Orefici** is the scientific coordinator of the DEVANI project. She worked for many years at the Italian National Institute of Health as Research Director and as Head of the Unit of Bacterial Respiratory and Systemic Diseases in the Department of Infectious, Parasitic and Immune Diseases. In 1986, she was appointed as the head of the WHO Collaborating Centre on Streptococci and Streptococcal Diseases and from 1997 up to 2005 was the Director of the WHO Supranational reference Center for Surveillance of Antimicrobial Resistance in *M. tuberculosis*. She participated as head of unit in several international and national projects on streptococci, mycobacteria and related diseases. She was also a member of the Italian Delegation at the European Pharmacopoeia Commission (1996-2007) and has been the Chairperson of the CEN technical committee TC/216 "Chemical Disinfectants and Antiseptics" since 1999.



**Dr Knud Poulsen** graduated as a molecular biologist in 1986 from Aarhus University, Denmark. He did a Ph.D. on bacterial IgA1 proteases and when Mogens Kilian was appointed professor in bacteriology at the Institute of Medical Microbiology and Immunology, Aarhus University Dr Poulsen joined his research group and has been an associate professor at the institute since 1991. He has been involved in different projects on bacteria that colonize humans. The bacterial IgA1 proteases and their role in infectious diseases including meningitis are still one of his major interests. Dr Poulsen has also worked on population genetics and phylogeny of different bacterial species including GBS, *Streptococcus pneumoniae* and *Aggregatibacter (Actinobacillus) actinomycetemcomitans*. For *A. actinomycetemcomitans*, he has contributed to

the identification and analysis of a particularly pathogenic evolutionary lineage, termed the JP2 clone, involved in aggressive periodontitis in adolescents of North and West African descent.



**Prof Claire Poyart** is Professor at the Cochin University Hospital in Paris and heads the Department of Bacteriology and the National Reference Centre for Streptococci. Her research focus is mainly on *Streptococcus agalactiae*, a major cause of invasive infections in the neonate. The main goals of her research activity aimed at elucidating the strategies used by GBS to adapt to hostile growth conditions, including those induced by the host immune system, and to adhere to and invade various epithelial cells to cause meningitis. Her team also developed molecular tools for GBS capsular typing, detection of virulence genes, and antibiotic resistance determinants.



**Prof Barbara Spellerberg** graduated from medical school at RWTH Aachen in Germany, in 1990. She was awarded a PhD in 'Lipolysis during methylxanthine therapy in neonates' in 1992 and obtained her habilitation on 'Streptococci in the interaction with eukaryotic structures: Identification of genetic determinants' in 1999. She was appointed as a senior lecturer for Medical Microbiology and Molecular Infectious Diseases at the Institute of Medical Microbiology at RWTH Aachen in Germany from 1999 to 2001. She is currently an associate professor of Medical Microbiology and Hygiene at the University of Ulm and has been a member of the graduation committee of the Medical faculty at the University of Ulm from 2002 to 2006. Her other previous appointments include; Research associate at the Institute of Medical Microbiology, RWTH Aachen; Medical

Microbiology Fellowship at the institute of Medical Microbiology, Postdoctoral Research Fellow at the Laboratory for Molecular Infectious Diseases, Rockefeller University, New York, USA; Paediatric resident and internship at the Children's Hospital of the RWTH Aachen in Germany.



**Dr John Telford** has a PhD in Molecular Biology from Zurich University. He has worked at Novartis Vaccines & Diagnostics in Siena for over 24 years in a number of roles, recently as Project Leader for GBS vaccines. He is currently Head of Microbial Molecular Biology overseeing antigen discovery for a number of vaccine projects including GBS.



**Dr Levantia Zachariadou** is the Associate Director of Medical Microbiology Department, at the “Aghia Sophia” Children’s Hospital, Athens, Greece. Her main topics of interest include beta haemolytic streptococci and urine infections in children. She has received training on conventional and molecular typing methods on *Streptococcus pyogenes* at the Department of Microbiology, Medical School, National and Kapodistrian University of Athens, Greece and at the Respiratory and Systemic Infections Department, Health Protection Agency Centre for Infections, London, UK. She was also a member of the StrepEURO Study group Programme (2003-2004) and has produced a number of publications as well as oral and poster presentations. She has attended a number of

workshops and training courses mainly on *S.pyogenes* but, also, on other beta haemolytic streptococci, urine and enteric pathogens, antibiotics and resistance mechanisms.

## Biographies of Administrators

**Mr Francesco Cavoto** owns the FRADEV Company and acts as IT Consultant and Webmaster at ALTA. He is responsible for web applications, software development, IT consulting and assistance; he is currently enrolled in the Science and Theory of Information Technology at the University of Siena (Italy).

**Dr Antonella Chiucciuini** is one of the Grants managers of ALTA (Siena, Italy), with experience in preparation and management of EU and internationally funded projects; she has a Degree and a PhD in Biological Sciences.

**Ms Laura Giordano** is Events assistant of ALTA (Siena, Italy), with experience in organization of National and International events and in administration of EU projects; she has a Degree in Science of Communication (University of Siena).

**Mr Francesco Grassiccia** is Graphic designer of ALTA (Siena, Italy), he is responsible for the conception, creation, and realization of graphic project: logo, leaflet, poster, brochure; he has a degree in Science of Communication (University of Siena).

**Miss Sophia Masud** is the UK Project Administrator for the DEVANI project. She is also involved within another EU funded project called DIPNET (European Diphtheria Surveillance Network). She has a degree in Business Studies.

# Abstracts



# Abstracts

Abstract 1.1

## GBS Overview: Victories and Vexations

Carol J. Baker

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Before the 1970's *Streptococcus agalactiae* or Lancefield group B Streptococcus (GBS) was considered a rare human pathogen, described in microbiology textbooks only as a cause of bovine mastitis. A decade later GBS had become recognized as the most frequent cause of early (< age 7 days) and late (age 7-89 days) onset pneumonia, bacteremia and meningitis in USA infants, and was accompanied by a case-fatality rate that ranged from 15-50%. Today the incidence and associated mortality of early-onset disease (EOD) has been reduced by ~75% in association with maternal antenatal culture screening and intrapartum penicillin prophylaxis, but GBS remains is the single most frequent pathogen causing bacteremia and meningitis in infants < age 3months.. Fortunately, GBS remains uniformly susceptible to penicillin and  $\beta$ -lactam antibiotics. By the 1980's GBS also was recognized as a cause of infections in pregnant women and non-pregnant adults, the latter typically with underlying medical conditions such as diabetes mellitus, heart disease or malignancy. Adult infections now account for two-thirds of the USA invasive GBS disease burden. While the transmission and pathogenesis is well-defined for EOD infections, those for LOD remain largely undefined. Two of several virulence factors have been defined for human infections, capsular polysaccharide (CPS) and  $\beta$ -hemolysin, and maternal delivery serum IgG specific for type III, and to a lesser extent types Ia and V, are associated with protection against infant EOD. The GBS serotype distribution of isolates causing EOD infant and pregnant women infections mimic each other and the only substantial change has been the appearance of type V strains in the late 1980's that resulted in a reduction in type II infections. Phase 1 and 2 trials of CPS-tetanus toxoid conjugate vaccines in healthy young adults (age 18-45 years) and the elderly document immunogenicity by functional CPS-specific assays, protection in murine models of infection and safety. Recent advances indicate that several GBS surface proteins could be useful either as protein carriers in conjugates or as "stand alone" vaccines. Furthermore, reverse vaccinology should speed development of new candidate GBS vaccines, but prevention of disease in infants will require partners in industry and consensus on appropriate target populations for clinical trials that will provide the greatest disease prevention.

Abstract 1.2

## Epidemiology of GBS and Screening Strategies

Monica M. Farley

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Group B streptococcus is an important cause of invasive disease in newborns and older adults. Women with vaginal or rectal colonization with GBS during the prenatal period have more than a 25 fold increased risk of delivering a infant with early-onset GBS disease. Other risk factors include preterm delivery, prolonged rupture of membranes, intrapartum fever and a history of previous delivery of an infant with invasive GBS disease. Invasive GBS infections are tracked in the U.S. by the CDC-sponsored, Active Bacterial Core Surveillance (ABCs) Program. Prior to the introduction of prevention guidelines in 1996, rates of invasive neonatal GBS disease ranged from 1.8-3 cases per 1000 live births, resulting in an estimated 7500 cases of neonatal GBS disease annually, with approximately 4% mortality. In 1996, guidelines recommending intrapartum antibiotic prophylaxis using either a risk-based or culture-based screening approach were issued in the U. S. The rate of early-onset GBS disease declined by 70%. Late-onset disease remained stable at approximately 0.35 cases/1000 live births. New guidelines recommending universal screening for vaginal and rectal GBS colonization of all pregnant women between 35-37 weeks' gestation were published in 2002. In ABCs data from 2000-2006, an overall 23% decline in early-onset neonatal GBS disease was noted; however, between 2003 and 2006, an upward trend in early-onset disease occurred, specifically among black term infants. Late-onset disease remained stable. The most common disease syndrome in early-onset disease was bacteremia (83%), 9% pneumonia and 7% meningitis. The percentage of infants with early-onset disease having a preterm delivery increased from 18 to 33%, although the GBS rate among preterm infants did not change significantly. Meningitis accounted for 26% of all late-onset neonatal GBS disease and overall mortality was 4.3%. Preterm birth was common (42%) among infants with late-onset disease and was associated with a higher mortality. Invasive GBS disease in non-pregnant adults doubled from 1990 to 2005 and represents a substantial burden, particularly in the elderly, blacks and adults with diabetes. Serotypes Ia, III, and V account for approximately 75% of early-onset, 89% of late-onset and 65% of adult invasive GBS disease. GBS isolates remain generally sensitive to penicillin, ampicillin, cefotaxime and vancomycin. Clindamycin and erythromycin resistance was 15 and 33% respectively in 2003 and associated with serotype V. Recommendations for universal screening were rapidly adopted in the U.S. with significant impact; but missed opportunities for prevention, particularly in preterm deliveries remain. New strategies, such as development of effective GBS vaccines, continue to hold the most promise for prevention of early-onset, late-onset, and possibly targeted non-pregnant adult disease.

Abstract 1.3

## Pathogenesis of GBS

Barbara Spellerberg

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*Streptococcus agalactiae* (GBS) is well-known as a neonatal pathogen causing sepsis, pneumonia and meningitis. In addition invasive infections among adult patients with underlying medical conditions appear to be rising. During the course of an invasive infection the bacteria have to adapt to different host environments, requiring the colonization of epithelial surfaces, the binding to extracellular matrix proteins, penetration of mucosal and cellular barriers and the evasion of innate and acquired host immune mechanisms. Numerous bacterial molecules participating in bacteria host interactions are required for the virulence of *S. agalactiae*. The polysaccharide capsule, the beta-hemolysin, surface molecules like the alpha-C-protein and the C5a-peptidase have been known and studied for many years. With the advent of whole genome projects, many additional bacterial molecules involved in pathogenesis have been characterized, including adhesins, invasins, immune modulins and novel bacterial organelles like pili. Analysis of numerous streptococcal genomes has also given us a glimpse to what extent horizontal gene transfer events between different bacterial strains and species occur and may be responsible for the ability of GBS to adapt to different hosts and environments. The progress in understanding complex host pathogen interactions will be crucial for the development of novel therapeutic and prophylactic strategies.

Abstract 1.4

## Clinical management of GBS diseases: a paediatrician's perspective

Maria Koliou

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Group B streptococcus is an important pathogen causing infection in children mainly neonates and young infants with significant morbidity and mortality. The vast majority of cases approximately 75% are of early onset disease manifesting within the first week of life while most of the remaining cases are late onset ie: occurring between 7 days and 3 months of age. A few cases can occur after the age of 3 months. About one percent of GBS invasive cases may reoccur.

After the introduction of recommendations for intrapartum antibiotic prophylaxis for mothers in labour at risk of transmitting GBS infection to their newborns the incidence of early onset disease has declined by about 80% in many countries. The current incidence of early onset GBS invasive disease in the USA is estimated to be 0.3 per 1000 live births. However, the incidence of late onset disease has not been affected. Diagnosis of an invasive GBS infection usually requires the isolation of the organism from an otherwise sterile site such as blood or the CSF or from a suppurative focus of infection such as pus in cases of arthritis. If the organism is isolated from surface cultures such as ear, umbilical cord or a gastric aspirate this does not document infection but only that the newborn has been exposed and has been colonised by the pathogen. Antibiotics given to mothers either for treatment or as intrapartum chemoprophylaxis may result in negative culture results of the newborn even if clinical signs of infection are present. Case fatality rates have decreased and currently are approximately 5% to 8% for early onset infection and 2% to 6% for late onset disease. Despite the rather low fatality rate some infants especially those with septic shock and some of those with meningitis may develop neurological sequelae. GBS disease remains a challenging disease with significant morbidity and mortality for young infants. The prevention strategies / interventions applied today have not managed to affect the decrease of late onset disease and have furthermore resulted in the administration of antibiotics to large numbers of women in labour and may contribute to some extent to the spread of resistance to antibiotics. The future advent of a safe and effective vaccine could well be the solution to this devastating disease especially for this very young and sensitive population of human beings. The currently recommended treatment regimens for the management of GBS invasive infection will be reviewed.

Abstract 2.1

## **Group B streptococcal invasive disease: a two-year survey by the French National Reference Centre for Streptococci**

Claire Poyart

National Reference Centre for Streptococci<sup>1</sup>, University Hospital Cochin-APHP<sup>2</sup>, INSERM 5673,  
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J. Raymond<sup>2,4</sup>, and P. Trieu-Cuot<sup>1,5</sup>

Group B Streptococcus (GBS) is the major cause of neonatal invasive infections but is expanding in non-pregnant adult, particularly in the elderly and patients with underlying diseases. Clinical data of 424 invasive infections and GBS were studied. All isolates were characterized by capsular molecular typing, PCR detection of the hypervirulent clone ST-17, MLST-typing, and antibiotic resistance. Among neonatal infection, 64% of the strains were from late onset infections, 75% were capsular serotype III, and the hyper-virulent clone ST-17 was recovered in 80% of meningitis. Among adult invasive infections, the mean age was 64 years and the main clinical manifestations were: primary bacteremia (46%), osteoarticular infections (27.7%), meningitis (8%), endocarditis (6%). Capsular serotypes III (28.4%), Ia (25.5%) and V (17.6%) accounted for the majority of the diseases. All strains were susceptible to beta-lactams, glycopeptides, and rifampicin. Tetracycline resistance was detected in 85% strains and erythromycin resistance was detected in neonatal (13.5%) and adult (25%) strains. In France, LOD account for the majority of neonatal invasive infections and the hypervirulent clone ST-17 is responsible for 85% of the meningitis. The aging of the French population provide an expanding number of patients at risk of GBS infections.

Abstract 2.2

## **Early onset group B streptococcus infections in Emilia-Romagna, Italy**

Dr Alberto Berardi

University of Modena, Modena, Italy

A Berardi<sup>1</sup>, C. Rossi<sup>1</sup>, L. Lugli<sup>1</sup>, R. Creti<sup>2</sup> and the Emilia-Romagna GBS prevention working group\*

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A. Zucchini, ML. Bidetti, A. Volta, MR. Rossi, G. Paltrinieri, G. Montini, C. Venturelli

Cases of Group B streptococcus (GBS) early-onset infections continue to occur, despite prevention. Since 2003 we conducted a prospective population-based study in Emilia-Romagna (an Italian region with a population of about 4,500,000) following the implementation of a screening-based approach. We involved all regional birth centres and 26 laboratories. Sixty-one early-infections were observed among 214,120 live births (annual disease incidence 0.28/1,000 live births). Among the 47 mothers of term infants, 41 (87.2%) had GBS antenatal screening, but only 10 of 41 were documented as group B streptococcus culture-positive. Nine newborns had culture-proven infection despite having received prophylaxis.

Most infections presented in infants whose mothers were screened group B streptococcus culture-negative. However, only 25.0% of mothers who should have been treated with antibiotics in labor received prophylaxis. Missed opportunities for prevention contributed more than prophylaxis failures to the early-onset disease burden.

Abstract 2.3

## ***Streptococcus agalactiae* in Greece; an overview**

Levantia Zachariadou

“Aghia Sophia” Children’s Hospital, Athens, Greece

*Streptococcus agalactiae* (GBS) is a major pathogen of concern in pediatric microbiological laboratories. During 2007, a threefold increase in the frequency of GBS early and late onset disease was detected at the “Aghia Sophia” Children’s Hospital, in comparison to the last eleven years. Most cases belonged to late onset disease (LOD) (>70%). In 2007, ten cases were detected amongst newborns and infants (ages ranged between 4 days to 3 months), which accounted for three times the mean annual number of cases identified between 1996-2006 (about 2.8 cases /year). During this period, GBS isolation rate of 0.32% was detected among all blood cultures examined, however in 2007, GBS isolation rate had increased considerably to 0.55%. Similarly, during 1996-2006 the GBS isolation rate from CSF increased to 0.74%, while in 2007 a much higher GBS isolation rate was observed (1.57%). GBS was isolated from two sites in eleven cases. A total of 34/41 GBS strains were serotyped. Serotype III was the most common serotype identified amongst GBS strains isolated from CSF (88.9 %), blood (76.0 %) and urine (66.7 %). Serotypes Ia and Ib were each detected from 3/34 GBS strains, whereas serotypes II and V were each identified from 1/34 GBS strains. Of 34 GBS strains tested, three were non-typable (NT). 12% of strains were resistant to erythromycin and 5% were resistant to erythromycin and clindamycin. The incidence of GBS infection, especially in neonates, need to be thoroughly evaluated in Greece, in order to allow the most appropriate preventive strategy to be selected.

Abstract 2.4

## **Changing epidemiology of invasive GBS disease in England and Wales**

Theresa Lamagni

Health Protection Agency Centre for Infections, London, UK

Theresa Lamagni, Karen Broughton, Androulla Efstratiou

Routine surveillance of laboratory-confirmed invasive group B streptococcal (iGBS) infections has identified some marked changes in the epidemiology of these infections during 1990s and 2000s. The overall rate of iGBS (all ages) increased year-on-year, standing at a provisional 2.9 per 100,000 population in 2008. Rates of early onset (0-6 days) invasive GBS disease showed no clear temporal trend, whilst rates of late onset disease (7-90 days) showed modest increases. The combined rate of early and late onset disease in 2008 was 0.69/1000 live births. Between 1995 and 2003, the proportion of iGBS reports in adults (over 15y) increased from 50-54% (1990-1995) to around 70% from 2003 onwards. Resistance to erythromycin increased during the 1990s and 2000s, from 1% to over 10% since 2005. Characterisation of isolates submitted to the national reference laboratory showed a relative stability of serotypes, with type III, Ia and V the top three ranking serotypes. As the leading cause of severe neonatal sepsis, the public health focus for GBS infection in the England and Wales has naturally been on infant disease, and whilst adult disease is increasing proportionally, the impact and opportunities for prevention continue to make this an appropriate focus of activity.

Abstract 3.1

## Overview of DEVANI

Graziella Orefici

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Invasive group B streptococcus (GBS) disease is still a leading cause of morbidity and mortality in the neonate. Neonatal GBS infection can result in sepsis, pneumonia or meningitis; no vaccine exists to prevent this disease. Approximately 15-30% of women are colonized with GBS. Despite the intravenous antibiotic prophylaxis (IAP) offered during labour to GBS positive mothers GBS disease still occurs in 0.68/1000 live births.

An effective vaccine administered to women could induce protective antibodies (IgG) to be passively transferred to newborn infants. Nine serotypes of GBS are known: Ia, Ib, II, III, IV, V, VI, VII and VIII. Since disease rates are too low to support conventional field efficacy studies, we have to base on correlative antibody levels.

Therefore current understanding of geographic serotype distribution and of antibody levels in maternal population is critical for designing a comprehensive vaccine. Novartis VD scientists have recently characterized three GBS proteins, identified as structural components of novel pilus-like structures. None of them is universally expressed by all strains but, in combination, may confer protection in newborn mice from immunized mothers against lethal challenge with different GBS. This observation suggests that a novel vaccine may include the three recombinant proteins together with CPS conjugates representing the major disease causing serotypes. Objectives of the project are:

- to identify the best candidate formulation(s), adjuvants and immunization schedules for a vaccine capable of inducing high titre durable antibody IgG responses in adult female mice.
- to identify the major GBS serotypes causing disease in newborns in Europe to assess which CPS conjugates need to be included in the vaccine.
- to assess the distribution of the genes encoding the pili protein antigens among strains from cases of disease and from carriers.
- to establish the level of maternal antibody titres against capsular polysaccharide and candidate protein antigens which correlates with resistance to GBS disease in the newborn.

Abstract 3.2

## GBS vaccine developments

John L. Telford

Novartis Vaccines and Diagnostics, Siena, Italy

We have taken a Reverse Vaccinology approach to the identification of protein candidates for inclusion in a vaccine against GBS disease. Starting from the complete sequence of the genomes of 8 strains of GBS representing the major disease associated serotypes we identified over 500 genes coding for proteins predicted to be exposed on the surface of the bacteria. Each gene was cloned and expressed in *E. coli* and the recombinant protein was used to immunize female mice. After mating, the pups were challenged with virulent GBS. From these studies, we identified a number of protective antigens. In particular, we discovered that the components of previously unrecognized pilus like structures. We have studied the sequence variation and expression of these structures in a large panel of GBS isolates from different geographic locations. The results indicate that a vaccine containing a combination of 3 pilus components would likely confer effective protection against most circulating strains of GBS.

Abstract 3.3

## **GBS: Screening, diagnosis and clinically relevant antimicrobial resistance**

Pierrette Melin

Centre national de référence des streptocoques B CHU de Liège, Liege, Belgium

In the setting of the successful implementation of the antenatal group B streptococcal (GBS) screening-based strategy for prevention of GBS neonatal diseases, efforts to improve screening for GBS status remain important. Critical factors that influence the accuracy of detecting GBS maternal colonization are the choice of culture media, the body sites sampled, and the timing of sampling.

Despite efforts related to sampling and culture procedures, false-negative GBS-screening contributing to continuing EOGBS cases and false-positive screening leading to unnecessary intrapartum antimicrobial-prophylaxis, occur. As GBS-carriage is highly variable, the predictive values of GBS antenatal cultures are not always good predictors of the maternal GBS status at presentation for delivery. Rapid non-cultural GBS screening methods, to perform at admission for delivery, have been developed: antigenic tests are not sensitive enough to replace antenatal screening cultures but available real-time PCR have fared better in the detection of GBS. Real-time PCR tests could improve effectiveness of the screening-based strategy and lead to a further reduction of the incidence of EOGBS disease. However questions of costs and logistics remain unanswered. The evolution of the different cultural or non-cultural options to improve the GBS-screening strategy will be reviewed.

Either for therapy or for intrapartum chemoprophylaxis, penicillin for its bactericidal activity and narrow spectrum, remains the agent of choice. For the true penicillin-allergic patients, clindamycin or erythromycin have been recommended as alternative drugs. However, probably as a consequence of the important use of macrolides, related drug resistance among streptococcal isolates is currently recognized. Epidemiology of resistance to antimicrobial agents will be presented.

Abstract 3.4

## **Overview of GBS molecular typing methods**

Knud Poulsen

Institute of Medical Microbiology and Immunology, Aarhus University, Denmark

Several different DNA based molecular methods have been applied to type GBS. DNA fingerprinting using PFGE analysis is a method that has often been used for epidemiological studies like evaluation of mother to child transmission. Multilocus sequence typing (MLST) is used to study global epidemiology of the species. MLST gives a measure of relatedness between isolates and therefore it is suited for inferring phylogeny, but a recent report on horizontal transfer of very large segments of the chromosome between strains and supported by complete genome sequences implies that results on evolution of GBS based on MLST should be revised. Molecular typing of individual genes or gene complexes has also been widely applied to GBS. Serotyping using specific antisera raised against the 10 recognized capsular serotypes of GBS has been the traditional method for typing isolates. Several DNA based capsular typing methods have been developed in recent years. These methods are convenient and allow typing of isolates that express very little or no capsular polysaccharide under laboratory conditions. Molecular typing methods have also been used to analyse the presence, absence, and allelic variation of putative virulence-associated genes.

Abstract 4.1

## ***Streptococcus agalactiae* Genomics and proteomics**

Philippe Glaser

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The complete genome sequences of eight *Streptococcus agalactiae* (GBS) are currently available. These eight isolates are of human origin, roughly covering the diversity present among human strains as defined by MLST studies. Genome comparisons allow thus both, intra- and inter clonal-complex comparisons. The first large comparison of 8 GBS genomes lead to the concept of the species pan genome that is constituted of a core genome shared by all isolates and a dispensable genome shared only by a subset of the isolates.

The proteomic complement of these eight isolates deduced from their genome sequences, allowed to infer their metabolic capacities as well as their repertoire of surface components. Analysis of the dispensable genome revealed that it corresponds mostly to mobile genetic elements, mainly Integrative and Conjugative Elements (ICEs) and phages and to putative antigen coding genes.

Moving from gene content analysis to the analysis of the distribution of nucleotide polymorphisms along these eight genomes allowed us to identify the recombination events, which lead to the presently observed genome organization. This analysis showed that each GBS genome is shaped by conjugative DNA exchanges involving chromosomal regions of more than 300 kb and highlights the role of ICEs in the evolution of GBSs. By tracing back the origin of each fragment, as a means to reconstruct the evolutionary history of the 8 human GBS genomes, we could conclude that these isolates might have derived from a human adapted strain, which has diversified through subsequent genetic exchanges with unrelated strains.

Taken together, GBS genomics brought unique information to understand host adaptation and evolution of GBS but also for the development of specific diagnostic tools and most importantly for the development of a universal GBS vaccine. Further proteomics studies will permit to strengthen these genome-based hypotheses.

# Poster Abstracts



# Poster Abstracts

Abstract P1

## Overview of group B streptococcal screening and laboratory diagnostics in Europe

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**Objectives:** Group B Streptococcus (GBS, *Streptococcus agalactiae*) is a leading cause of neonatal sepsis, meningitis and pneumonia in industrialized countries affecting 1-2 newborns/1000 live births in Europe. The DEVANI (DEsign of a Vaccine Against Neonatal Infections) study, which is a pan-European programme funded through the European Commission Seventh Framework is coordinated by Novartis Vaccines & Diagnostics, Siena, Italy, and includes Public Health Institutes and Universities from eight European countries. The overall objective of this project is to design and develop a new vaccine for the prevention of neonatal GBS disease through the transfer of antibody from the mothers to the foetus during the last weeks of pregnancy. The DEVANI project is organised into eight work packages, one of which is the work package for Method Standardisation and External Quality Assessment (EQA) schemes (work package 6). One of the first objectives of this work package was to undertake a questionnaire-based surveillance amongst all DEVANI participating countries to assess microbiological procedures for GBS screening, diagnosis and typing.

**Methods:** A questionnaire was sent to eight DEVANI participating centres on the 28th April 2008. All centres completed and returned their questionnaire by 16th May 2008.

**Results:** Currently European countries within the DEVANI consortium that do not offer routine screening for GBS are the United Kingdom, Bulgaria and Denmark. The majority of centres tend to use culture based methods for GBS screening and confirmation (7/8 centres), although non-culture based methods are also used by 5/8 centres. Almost all centres (7/8) serotype GBS isolates using the Strep-B Latex kit (Statens Serum Institut, Denmark) and 5/8 centres also use molecular typing methods such as, a Multiplex PCR Assay, Multilocus Sequence Typing (MLST) and Pulse Field Gel Electrophoresis (PFGE).

**Conclusions:** There are limited data in Europe on GBS disease and its preventative strategies. This questionnaire-based surveillance has determined the current laboratory capabilities and status for GBS characterisation as well as potential GBS screening procedures within the DEVANI consortium.

Abstract P2

## Impact of antenatal screening on neonatal Group B streptococcus early-onset disease

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**Objectives:** to understand the impact of antenatal screening and intrapartum prophylaxis on the clinical presentation of neonatal Group B streptococcus (GBS) infections during a 66 months period.

**Methods:** prospective, population-based study in Emilia-Romagna (Italy) between 2003 and 2008, after the adoption of a screening-approach. Record of invasive group B streptococcus infections among infants aged <7 days.

**Results:** Sixty-one early-infections in the period. Only 29.8% mothers GBS culture-positive (table 1). Nine infants of lower gestational age (< 35 weeks of gestation), with 3 deaths, 6 mechanical ventilations and 7 catecholamine supports. Low disease severity among 9 infants receiving intrapartum antibiotics. Four of 6 meningitis found among infants whose mothers received no prophylaxis because of negative GBS screening and no risk factors.

**Conclusion:** Higher disease severity was among infants of lower gestational age (not eligible for antenatal screening). Less predictable infections and most meningitis were observed in infants born to mothers GBS culture-negative at screening and without risk factors. The microbiologic screening failure was the main cause of neonatal disease persistence.

Table 1: Characteristics of population in study

Variables	
<b>Incidence data:</b>	
Total live births in region, n	214,120*
All preterm births, n ( % of all regional live births)	15,756 (7.36%)*
Neonatal infections, n (incidence per 1,000 live births)	61 (0.28)
At term neonatal infections, n (incidence per 1,000 of regional term births)	47 (0.24)
Preterm neonatal infections, n (incidence per 1,000 of regional preterm births)	14 (0.89)
<b>Study group:</b>	
Neonatal gender, m/f	33/28
Mothers with ≥1 risk factors, n (%)	26 (42.6%)
Known maternal GBS status, n (%)	47 (77.0%)
GBS culture-positive mothers, n (%) §	14 (29.8%)
Mothers delivering at term who had antenatal GBS screening (35-37 weeks) n (%)	41 (87.2%)
Mothers delivering at term who were GBS screened culture-positive, n (%)	10 (24.4%)

\* Data obtained from Regional Health Agency hospital discharge charts

§ Three mothers, preterm delivering (< 35 weeks), were screened during labor

Abstract P3

## Reference typing of *Streptococcus agalactiae*: can we improve the non-typability rates of UK isolates?

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**Objectives:** The National and WHO Streptococcus and Diphtheria Reference Unit receive over 400 isolates of *Streptococcus agalactiae* (Lancefield Group B streptococci (GBS)) for serotyping per annum, predominantly from sterile sites. Of these, 6 to 10 % were non-typable using Lancefield extraction of the antigens followed by immunodiffusion using in-house antisera. Our objective was to reduce this percentage of non-typable GBS.

**Methods:** All isolates from 2006 and 2007 that were non-typable using Lancefield extraction of the polysaccharide antigens followed by immunodiffusion using in-house antisera, were examined using the Strep-B-Latex slide agglutination test (Statens Serum Institut, Denmark) using a modification of the method. A suspension of GBS, from an overnight culture on Columbia blood agar, was made in 250 µl saline. A drop of this suspension was mixed with a 1 µl loopful of Statens Serum Institut group B latex reagent on a glass slide. This was read immediately for agglutination.

**Results:** During 2006 we received 426 isolates of GBS for serotyping. Of these, 45 (10%) were non-typable using Lancefield extraction of the antigens followed by immunodiffusion using in-house antisera. Non-typability was reduced to 3% (12 isolates) using the Strep-B-Latex slide agglutination test.

In 2007, 378 Group B isolates were tested in parallel by using both methods. Non-typability by Lancefield extraction amounted to 25 isolates (6%) and decreased to 16 isolates (4%) using the latex test. In September 2007, a new serotype IX was proposed and all non-typable GBS from 2006 and 2007 were examined for the presence of this new serotype

**Conclusion:** The use of the Strep-B-Latex slide agglutination test (Statens Serum Institut, Denmark) has significantly reduced the non-typability rates of UK GBS isolates. We are now using the Strep-B-Latex in our laboratory as the primary test for the serotyping of GBS isolates.

Abstract P4

## Group B streptococcal invasive disease in adult in a six year surveillance in Hospital Virgen de las Nieves (Granada, Spain)

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Group B streptococcus (GBS, *Streptococcus agalactiae*) invasive infections in non pregnant adults are increasing according to different reports, particularly in the elderly and patients with underlying diseases.

**Objective:** We describe the trend in the incidence and the clinical characteristics and outcome of the disease.

**Methods:** This study was conducted between 2002-2007, the infection was diagnosed in basis isolation of GBS sterile environment (blood, CFS, sterile liquid) or biopsy tissue. GBS was identified by usual procedures. The clinical history of patients was revised.

**Results:** 97 patients were identified. The mean age of the patients was 61.5 years. Relation M/F 47/57. The biannual cases were 23 (2002-2003), 50(2004-2005), 24 (2006-2007)  $p < 0,001$  in compared years. Only ten patients did not present any underlying disease. 29 had 1, 50 had 2, 7 had 3, 1 had 4, being the diabetes 30%, surgery 29%, cancer 11%, cardiovascular disease 7%, alcoholism 5% most important. GBS was found in 38 cases of biopsy, 20 cases of abscess, 25 hemoculture and 14 sterile liquid. Clinical diagnosis was 51% infection tissue and bone, 22% primary bacteraemia and 9 peritonitis. In total nine patients died.

**Conclusion:** The incidence presents peaks to compare this period of study biannually, but non increasing in years studied. Above all affecting older people with debilitating diseases. This population group will benefit from the development of the vaccine against GBS.

Abstract P5

## GBS serotypes from invasive neonatal disease or maternal carriage. The Italian experience

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One of the most important factors involved in the virulence of group B Streptococcus (GBS) is the capsule polysaccharide of which, in addition to nine antigenic variants (Ia, Ib, II to VIII), the serotype IX has been very recently identified.

A national surveillance on the neonatal invasive GBS disease and maternal carriage started in 2005 as a regional study and it has been implemented by the participation of 10 hospitals located both in the northern and southern Italy since 2007. The analysis of serotype distribution demonstrated the predominance of serotype III among neonatal infections (65%) while serotype III and not typable strains were the most diffuse among pregnant women in a comparable proportion (34%), followed by serotype V (13%). Although GBS infection is not a notifiable disease, the organization of this hospital network has enhanced the awareness and the attention among clinicians on the GBS disease.

Abstract P6

## Non-Culture diagnosis of neonatal infections caused by *S. agalactiae*

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Group B streptococci (GBS) are the main cause of life-threatening infections in newborn babies in the UK. Infections in babies are classified into early-onset (EOD) (0-6 days old) and late-onset (LOD) (7-90 days old) disease. In 2007, disease rates reported were 0.37 per 1000 live births for EOD and 0.24 per 1000 live births for LOD. The use of conventional methods to diagnose infection in newborns is unreliable therefore rapid, reliable and sensitive methods are needed for detection of GBS bacteraemia in neonates.

We report the use of a real time PCR assay targeting the *cylB* gene (involved in haemolysin activity) and an internal processing control (IPC) was introduced to highlight amplification failure due to inhibition.

Hundred and six clinical samples were analysed. Ninety one were from babies who had suffered sudden unexpected death in infancy (SUDI) (several sample from each patient were tested) and the remaining were from neonates with query GBS sepsis or meningitis.

Amongst the babies who had suffered SUDI, eight sample were positive by PCR, (four patients) and amongst the neonates with clinical sepsis and meningitis, four were positive (four patients)

The assay is reproducible, sensitive and rapid. The use of an IPC with the same primers as the target, increases throughput and reduces cost.

Abstract P7

## Distribution of serotypes of clinical group B (GBS) streptococci newborn and pregnant women in Andalusia (Spain)

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GBS is a major cause of severe neonatal invasive diseases and pathogenic in pregnant women and adults population. The serotypes Ia, Ib, and III caused the majority of diseases. The developed future vaccine need to know current serotypes circulating

Objective: To know the serotypes circulating in our population.

Methods: from May 2007 to October 2008 we have serotyped 14 strains GBS invasive (11 early-onset and 3 late onset) and 150 strains of pregnant women using the Strep-B-Latex slide agglutination test (Statens Serum Institut; Denmark) but using a modification of the method (Efstratiou Method). A suspension of GBS from an overnight culture blood agar was made in 250 µl saline solution. A drop of this suspension was mixed with a 1µl loop of Statens Serum Institut group B latex reagent on a glass slide.

Result: Among isolates from neonatal early onset type Ia (5/11) was the more common, type III (4/11) and type IV (2/11). For 3 late onset infection the distribution was type Ia (2/3) and type III (1/3). Among pregnant women the type III was more common 50/150, type Ia 38/150, type V 21/150, type II 15/150, type IV 11/150, non typable 10/150 and type VII 3/150.

Conclusion: Compared with previous study in our population we noted an increase of serotypes IV and V in colonization of women pregnant.

Abstract P8

## Prevalence of haemolytic streptococci in pregnancy

Wythenshawe Hospital Manchester, UK  
(Interim analysis)

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Introduction and Purpose of study: Invasive group B streptococcus (GBS) disease is a leading cause of morbidity and mortality in neonates and other high-risk groups. The UK does not have a national screening programme for GBS carriage in pregnancy, hence colonisation rates are unknown. It is standard practice to offer intra-partum antibiotic prophylaxis (IAP) during labour to colonised women, leading to reduced incidence of neonatal GBS disease.

It is rare to find data about the prevalence of other haemolytic streptococci in pregnancy including Group A Streptococcus (GAS) (*Streptococcus pyogenes*) despite suggestions of increasing importance in pregnancy and neonatal period.

Our study aims to investigate the carriage (colonisation) of haemolytic streptococci groups A, B, C and G in pregnancy.

Methods: Swabs were taken from the throat, vagina and rectum of pregnant women at 34 - 40 weeks of gestation and inoculated onto Horse blood agar, Staph-Strep selective agar and into a selective Todd Hewitt broth. Plates were incubated anaerobically for 18 to 24 hours. All beta-haemolytic streptococci were grouped by slide agglutination. Plates that were negative at 24 hours were re-incubated anaerobically for a further 24 hours. Group B streptococcal isolates were further characterised.

Results: Interim analysis: a total of 70 women were recruited into the ongoing study. Seven (10%) women had GBS from rectum and 8 (11%) from VS. A detailed discussion and conclusions will be presented during the poster session.

Abstract P9

## **A multiplex PCR assay for the direct identification of the capsular type (Ia to IX) of *Streptococcus agalactiae***

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A multiplex PCR assay for the identification of serotype Ia to IX of *Streptococcus agalactiae* (GBS) was developed. By using a single PCR reaction containing a mix of 19 primers, the assay identified all serotypes through the analysis of the unique two or three band pattern on agarose gel, offering a fast and accurate way for the cps type determination by a method easily reproducible in any laboratory with a molecular biology facility. A collection of GBS clinical strains was analyzed for assessing the reliability of the multiplex PCR assay by comparing the cps typing assignment with the serotyping results obtained by the latex agglutination test. In case of non congruent results, the repetition of the phenotypic test or the use of an alternative molecular assay, as the RFLP of the GBS capsular gene cluster, confirmed the results obtained by the multiplex PCR assay. The assay also enabled the unambiguous cps type assignment of 36 strains classified as non typable by the phenotypic method.

Abstract P10

## **Group B Streptococci from invasive infections in Denmark 2003 to 2008**

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**Objectives:** To characterise group B streptococci (GBS) that caused severe invasive disease in Denmark. National laboratory surveillance was carried out to describe the circulating streptococcal isolates.

**Methods:** Invasive GBS isolates were received from Clinical Microbiological Departments and B-serotyped using agglutination test with GBS latex and Lancefield precipitation tests with type specific antisera (SSI Diagnostica, Denmark). For isolates from newborns (<90 days) sequence type (ST) using multi locus sequence typing were determined. In addition isolates were tested for susceptibility to erythromycin, clindamycin, tetracycline and oxacillin using disc and Etests.

**Results:** In 2003 to 2008, 574 invasive GBS isolates were received of which 19% (110) were from newborns. Of all GBS isolates 34% were serotype III, 16% serotype V and 16% serotype Ia. Among newborns 62% were serotype III and 16% serotype Ia and the dominant sequence type among typed isolates was ST17. In 2006-2008, 5% of all GBS isolates were erythromycin resistant, 3% clindamycin resistant and 5% tetracycline resistant.

**Conclusions:** The most frequent type among all isolates was serotype III. Among newborns the most frequent type was serotype III, ST17. The proportion of antibiotic resistant isolates was low.

Abstract P11

## **Streptococcal recombinant peptide vaccine as an alternative to conjugate vaccine development**

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Group B streptococcus (GBS) is an important human pathogen and common cause of newborn mortality. Considering polysaccharide capsule as the main GBS virulence factor several polysaccharide or conjugated protein- polysaccharide experimental vaccines had been created. Clinically accepted vaccine development is impeded by the factor of polysaccharide immunogenic variability and low immunogenicity. We suggest the usage of 3, or 4 component polypeptide vaccine based on the immunogenic epitops of the GBS surface proteins. Careful selection of polypeptides generated after cloning of the DNA fragments of the genes under study in the expression vectors allowed composing a three component peptide experimental vaccine providing protection against the variety of GBS serotypes employing several in vitro and in vivo methods. Side by side comparison of type III polysaccharide conjugative vaccine to the recombinant peptide vaccine could not distinguish which one was better even against type III GBS strain. In addition to the GBS, recombinant peptide vaccine was protective against Group A streptococcus (GAS) belonging to different M serotypes. Study of the epitope structure on one of the proteins included in the vaccine ScaAB allowed selecting immunogenic regions on the protein capable to elicit opsonising immunoglobulins against GBS and GAS.

Abstract P12

## **Intrapartum Group B streptococci detection by rapid polymerase chain reaction assay allows for timely antibiotic prophylaxis to prevent neonatal sepsis**

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**Objectives:** To assess whether a rapid PCR is reliable when performed in the labour suite by non-laboratory staff, and if it allows correct implementation of antibiotic prophylaxis.

**Methods:** We obtained antenatal and/or intrapartum recto-vaginal swabs in 695 pregnant women. Swabs were tested for GBS by culture. Intrapartum swabs were tested by PCR performed immediately by midwives. In a subset of women, a second PCR was performed in parallel in the microbiology laboratory.

**Findings:** Prevalence of intrapartum GBS colonisation was 19.3% according to culture. Using intrapartum GBS culture as the gold standard, assay sensitivities were 81% for ante-partum culture, 85% for midwife-performed PCR, and 95.7% for the laboratory PCR. Ten percent of women did not have intrapartum testing mostly due to advanced labour. GBS-positive colonisation (n=107) was known at least 4 hours before delivery in 68 (64%) and 73 (68%) women based on antenatal culture and PCR, respectively. Among 43 women delivering preterm, correct status was known at least four hours before delivery in 10 (23%) and 32 (74%) according to antenatal culture and PCR, respectively.

**Interpretation:** Intrapartum screening for GBS is feasible and at least as accurate as antepartum screening, even when performed by non-laboratory staff.

Abstract P13

## **Detection of Sip and ScpB Genes and Comparison of two Capsular Serotyping Methods among a Belgian Collection of Streptococcus agalactiae Isolates from invasive human diseases**

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Background: Group B streptococcus (GBS; *S.agalactiae*) is the leading cause of life-threatening bacterial infections in newborns. It's also responsible for significant morbidity-mortality in pregnant women, and non pregnant adults (NPA). Nine capsular polysaccharide serotypes (CPS) have been described. Vaccination of young women is expected to be the best long-term preventing strategy to protect their neonates against GBS invasive diseases. The first vaccinal approaches in development are CPS-based, conjugated-form or not. But, several GBS surface proteins represent a very promising immunogenic alternative to CPS to include in vaccines.

Objectives: The aims of this work were to check the presence of genetic determinants of two highly conserved GBS surface proteins Sip and ScpB, and to compare two capsular serotyping methods: a conventional agglutination test versus a multiplex PCR assay.

Materials and Methods: A total of 58 invasive GBS isolates were studied: 38 recovered in Belgium from neonates and 20 from NPA between 2005 and 2007. Specific PCR assays for identification of genes encoding GBS surface proteins including Sip and ScpB were carried out. The serotype determination was performed by a latex agglutination test (LAT) using a commercial kit, Serum Staat Institute (Denmark). All isolates were also submitted to a multiplex PCR assay for capsular typing of GBS as described by Poyart C. et al, 2007.

Results: All the isolates showed amplification of the expected DNA sequences of sip and scpB genes. Among the isolates, based upon the LAT, 9 strains belonged to serotype Ia, 5 to Ib, 4 to II, 25 to III, 4 to IV, 6 to V, 2 to VII and 3 isolates remained non typable. Compared to the multiplex PCR assay for capsular typing, discrepancies were observed for 17 % of the isolates.

Conclusions: 1) High molecular conservation of the genetic determinants of Sip and ScpB proteins were confirmed in this collection 2) Studies of Sip and ScpB protein expression would be mandatory 3) Use of a PCR capsular typing assay showed discrepancies when compared to LTA, a more extensive analysis and standardization of CPS typing methods are needed.

Abstract P14

## **Czech neonatal GBS from 2003 till 2008**

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In the last five years GBS isolates from 396 neonates have been received in the Czech NRL for Streptococci and Enterococci; 38 out of this number from blood and/or CSF. There has been a nationwide recommended preventive program in place since 2005; incidence of GBS EOD has been decreasing. In 2007 enhanced sentinel surveillance was introduced together with a detailed questionnaire focused on both mother and child's clinical conditions. All isolates have been serotyped, molecular characteristics and antibiotic resistance have been tested on selected ones.

Majority of isolates from blood/CSF were of serotype III (65.8%) whereas this serotype was much less pronounced for non-invasive isolates (25%). Vast majority of invasive isolates was covered by ST17, ST19 and ST23. There were no particular serotypes or ST outstanding among isolates from babies whose mothers received antibiotic prophylaxis in comparison to those who did not. We did not find any significant difference amongst premature and full-term neonates in terms of serotype or other attributes studied so far. Part of this investigation has been funded by a grant No. 9432/3 of the Internal Grant Agency of the Czech Ministry of Health.

Abstract P15

## **A comparison of real-time PCR and conventional culture-based methods for the direct detection of group B streptococci from clinical specimens**

Anna Vickers

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Group B streptococci (GBS) are the principal cause of sepsis and meningitis in neonates. Conventional culture-based methods for GBS detection are lengthy and can be unreliable. Development of more rapid and sensitive methods to detect GBS from clinical specimens may improve healthcare for expectant women and newborns. The objective of this prospective study was therefore to evaluate the utility of a non-culture based method for GBS diagnosis.

Mother and newborn pairs were recruited at two hospitals in the UK. Maternal vaginal/rectal swabs and neonatal ear swabs were examined for GBS by culture on Granada agar and with a GBS-specific real-time LightCycler.

Seventy-nine swabs were analysed. Culture and PCR methods were positive for nine specimens (five vaginal/rectal swabs and four ear swabs) and negative for fifty-six specimens (seven vaginal/rectal swabs and forty-nine ear swabs). For two vaginal/rectal swabs and six ear swabs, GBS were detected by PCR, but not by culture. Conversely, three vaginal/rectal swabs and three ear swabs were negative for GBS by PCR, but positive by culture.

Since the PCR-based method gave a positive GBS result for eight specimens that were GBS-negative by culture, this molecular technique could improve diagnosis and disease management, if employed alongside conventional detection methods.

Abstract P16

## **Interrogation of GBS ST-17 random insertion mutant banks**

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Group B streptococcus (GBS) is the leading cause of infection in newborn babies in the UK. A subtype of GBS (ST-17), is responsible for much of the disease observed, yet the reason why ST-17 is so over-represented in neonatal disease remains unclear. Phenotypic analysis of isogenic mutants alongside their respective "parental" strain enables the identification of important areas of the genome responsible for causing disease. We have investigated the potential for generating resources with which to readily identify virulence mechanisms and markers in ST-17 GBS. Clinical GBS ST-17 isolates were chosen from cases of early and late-onset of neonatal disease. Strains were transformed with pG+host9::ISS1 and random chromosomal integration confirmed. Approximately 9600 individual mutant colonies were gridded into microtitre trays. From this position it is possible to screen the mutant bank either phenotypically eg test the ability to grow in defined / supplemented growth media, or, genotypically eg identify mutants with ISS1 insertions within particular genetic loci. We have found the isolation of mutants in defined loci by genotypic screening is significantly more time-efficient than allelic exchange methodologies currently available for streptococci.

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