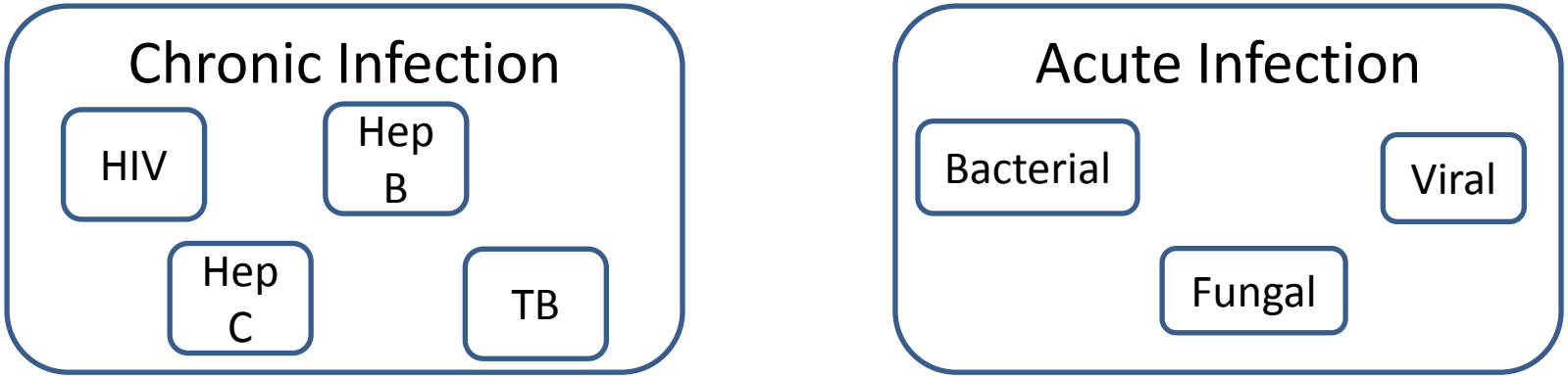
PENTA-ID

Prof Mike Sharland

PENTA-ID Expertise and Interests



Grants and project management

Study methodology and statistics

Regulatory and ethics issues

Microbiology/virology methods

Immunologic response

Pharmacology – PK/PD

Training and education

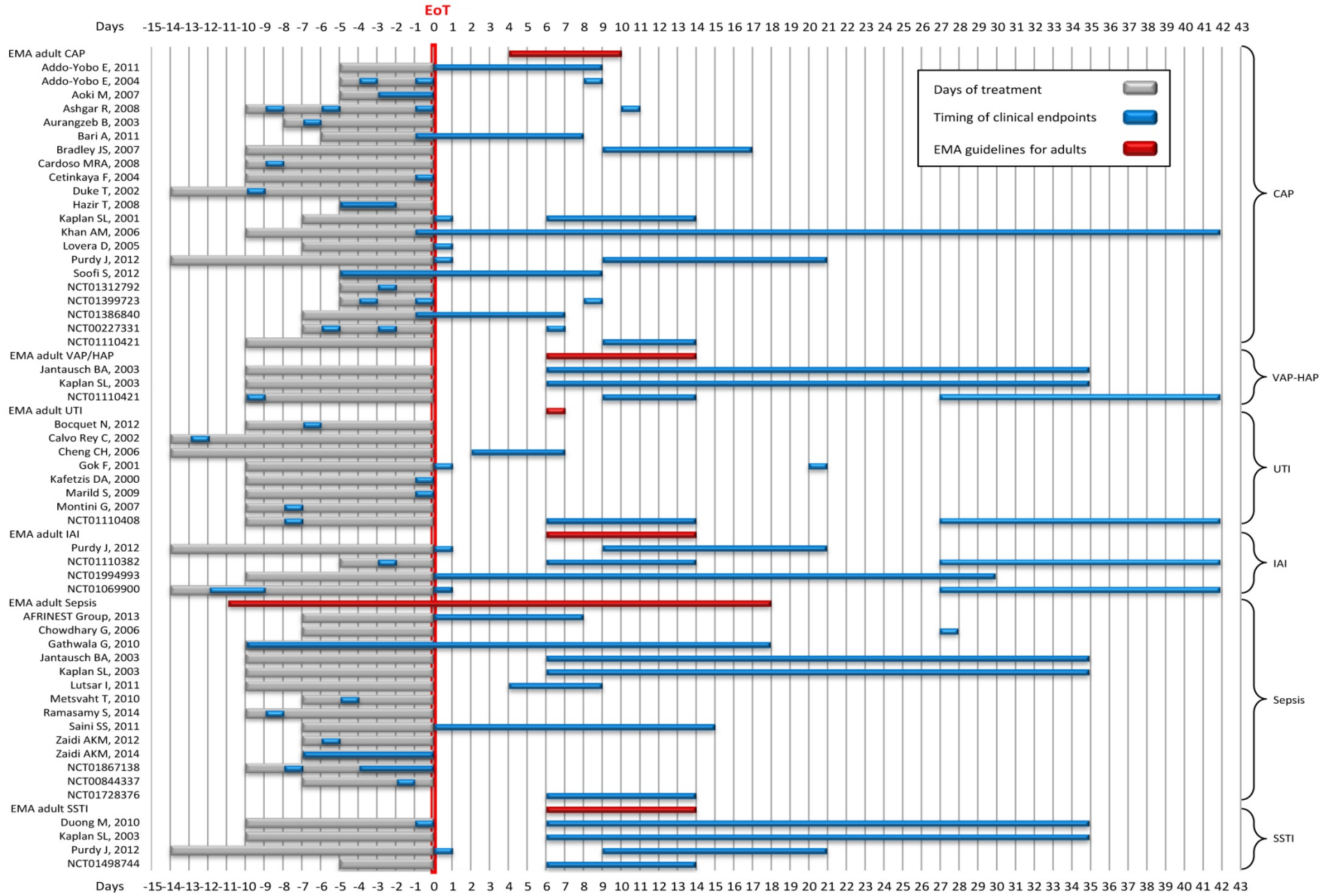
P-ID Acute infections

- Antibiotics
- Antivirals
- Antifungals
- Antimicrobial resistance

Investigator led Antibiotic trials

- Neonatal sepsis – strategic trials - NeoMero; NeoVanc
- CAP - Effective Management of Paediatric Acute Respiratory Infection – Horizon 2020
- Large pragmatic RCT comparing narrow vs broad empiric antibiotic prescribing strategies
- Other strategic trials – NIH, NIHR, EU - Drug/Dose/Duration

P-ID review of Paediatric Antibiotic CT's 2000-2014



Pharma led antibiotic trials

- Significant antibiotic pipeline
- Defined Clinical Infection Syndromes
- CAP/HAP/VAP/cSSTI/cUTI/cIAI (sepsis)
- No EMA/FDA Guidance on paediatric antibiotic trials – (EMA 2012 medicinal products to treat bacterial infection – EMA addendum 2013)
- Virtually no observational data to power future trials

GRAM-POSITIVE FOCUSED

Antibiotic	Drug class	Developer/owner	Status @ Sept 2014
Ceftaroline	Cephalosporin	Forest/AstraZeneca	Licensed for CAP & SSSI EU & USA - Broad spectrum (ceftriaxone + MRSA cover)
Ceftobiprole	Cephalosporin	Basilea	Licensed for CAP & HAP, not VAP – Broad spectrum – like cefepime + MRSA cover
Telavanvin	Glycopeptide	Astellas	Licensed, now marketed by Clinigen
Oritavancin	Glycopeptide	The Medicines Co	Licensed in USA for SSSI, EMA licensee applied for
Tedizolid	Glycopeptide	Pfizer	Licensed in USA for SSSI, EMA licensee applied for (previously called Dalbavancin)
Torezolid	Oxazolidinone	Cubist	Phase III SSSI complete, license applications pending
WCK-771	Quinolone (active isomer of nadifloxacin)	Wockhardt	QIDP status granted in US
BC-3781	Pleuromutilin	Nabriva	Phase II SSSI complete & successful
OP0595	b-lactamase inhibitor	Meiji	Phase I
Zambofloxacin	Quinolone	Pacific Beach	One phase III COPD trial complete
Solithromycin (CEM-101)	Ketolide	Cempra	Phase III CAP & gonorrhoea trials initiated
Delafloxacin	Quinolone	Melinta	First Phase III SSSI trail complete, second in progress, also trial vs gonorrhoea

GRAM NEGATIVE FOCUSSED

Antibiotic	Drug class	Developer/owner	Status @ Sept 2014
S-469266	Catechol cephalosporin	Shionogi	Phase I
POL-7080	Peptide	Polyphor (Roche)	Taken over by Roche- Phase II CF and VAP trials initiated
Aztreonam-avibactam	Monobactam-BLI	AstraZeneca	Phase I via IMI
Ceftazidime-avibactam	Cephalosporin+BLI	Novexel – Now taken over by AZ	Phase III cIAI & cUTI complete, limited license now from FDA on phase 2 data
Ceftolozane-tazobactam CXA-201	Cephalosporin/tazobactam	Calixa (acquired by Cubist – now Merck)	Phase III cIAI & cUTI complete, licensed for these CIS in USA
Plazomicin (ACHN490)	Aminoglycoside	Achaogen	Phase III bacteraemia trials started;
Debio 1450	FabI inhibitor	Debiopharm	Phase I (mecillinam activity vs EB)
Eravacycline (TP-434)	Tetracycline	Tetraphase	Phase III cUTI and cIAU trails in progress
Ceftaroline-avibactam (NXL104)	Cephalosporin+b-lactamase inhibitor	Cerexa/Forest/AZ	Completed phase II
Imipenem-MK7655	Carbapenem-inhibitor	Merck	Phase II in cUTI and cIAI

GARPEC Global Antibiotic Resistance, Prescribing, and Efficacy Among Neonates and Children

A global surveillance network focused on collection of data on neonatal and pediatric antimicrobial prescribing and resistance

Acute viral infections Investigator led

- PREPARE – FP7 - funds for 5 years a network of 20 large European children's hospitals
- Will capture data on hospital structure, workload, range of clinical infection syndromes
- PREPARE will provide largest pan-European cohort on range of acute viral infection (EV, RSV, FLU) with antiviral pipeline

Table 3: Overview of RSV antivirals, therapeutics and vaccines in clinical trials

Antivirals							
Type	Drug Candidate	Company	Target	MOA	Route of administration	Development Status	Results Summary
Antibodies	RI-002 (previously RI-001)[42]	ADMA Biologicals Inc	Various viral epitopes	Polyclonal RSV neutralizing antibody	IV	Ph3c	Significant improvement in RSV titer from baseline to D18; 9.24x in high dose group (n=21)[42] Compassionate Use (n=13): 4x rise in antibody titers[64]
	Motavizumab (MEDI-524)	MedImmune	F	RSV neutralizing monoclonal antibody	IV	Interrupted	Non-inferior to palivizumab, ↑ AE[32]
	Motavizumab-YTE (MEDI-557)	MedImmune (AstraZenica)	F	Triple Fc region mutation (YTE) humanized RSV neutralizing monoclonal antibody	IV	Ph1c	Half-life 2-4x longer than motavizumab (extended half life of 100 days)[66] RSV neutralizing activity persisted 240 days (v. 90 days motavizumab[66,67]
	MEDI-8897 (AIMM D25)	MedImmune (AIMM Therapeutics)	Prefusion F	RSV neutralizing monoclonal antibody	IM/IV	Ph2	Ongoing RCT in healthy preterm infants[68]
	ALX-0171	Ablynx	F	Antibody nanobody	Inhalation	Ph1	In healthy males: No dose-limiting toxicity, no significant change lung function, opportunity for once daily dosing[66] Ph1 ongoing in toddlers and infants with RSV LRTI[67]
	REGN-2222	Regeneron	F	Monoclonal antibody anti-RSV F	IM	Ph3	Recruitment to start June 2015[69]
Anti-sense	Asvasiran Sodium (ALN-RSV01)	Alnylam Pharmaceuticals	N	Small-interfacing RNA's (siRNA)	Intranasal	Ph2 c	Safe & well-tolerated in health adults[52,53] Ph2a Experimental Infection: 40% relative reduction in infection rate (P<0.01) [50,51] Ph2a Lung Transplant: 85% reduction in Bronchiolitis Obliterans Syndrome (BOS) (P<0.02)[55] Ph2b: Treatment effect D90 and D180 BOS 52-65%[52,54]
Fusion Inhibitors	TMC353121	Tibotec Pharmaceuticals/ Johnson & Johnson	F	Prohibits Cell entry	IV	Ph1	Not published[55]
	MDT-637 (VP014637)	Teva Pharmaceuticals (MicroDose Therapeutx)	F	Prohibits Cell entry	Inhalation	Ph2	No significant AE in all 3 phase 1 trials (single & multiple dose in healthy adults or single dose in asthmatics), desirable pharmacokinetic profile[56,58]
	GS-5806	Gilead	F	Prohibits Cell entry	Oral	Ph2	Achieved lower viral load, lower mucus weight, lower symptom scores; AE include low neutrophil counts and ↑ alanine aminotransferase[22,60]
	AK0529	Arkansas Biosciences Institute	F	Prohibits cell entry	Oral	Ph1	Ph1 ongoing[61]
Small Molecules	ALS-008176	Alios Biopharma Inc	RSV polymerase	Nucleoside analog	Oral	Ph2	Good safety profile, rapid decline of viral load and clearance of RSV RNA, decreased mucus weight and symptom score in healthy adults[62] Ph1 ongoing in RSV hospitalized children[62]
	Danirixin (GSK1325756)	GlaxoSmithKline (GSK)	CXCR2	Selective, reversible CXCR2 antagonist	In vitro	Ph1	Trial evaluating concentration necessary to inhibit neutrophil activation after in vitro whole blood incubation[50,51]
	RV568	Respivert Ltd		Narrow Spectrum Kinase inhibitor, inhibits viral replication	Intranasal	Ph1	Ph1 results not published[67,68]
	RSV604 (A-60444)	AstraZenica & Novartis	N	Inhibits RNA viral polymerase	IV	Ph2	Viral load and symptoms reduced in stem cell transplant patients with RSV infection reaching EC_{90}[66]

European Paediatric Mycology Network

towards a better understanding and management

Aims

- ✓ to investigate the clinical epidemiology of invasive fungal infections in neonates and children
- ✓ to create a forum for educating and training colleagues in the field of paediatric mycology
- ✓ to investigate new diagnostic and treatment modalities in specific paediatric patient groups

Pharma led– PIPs

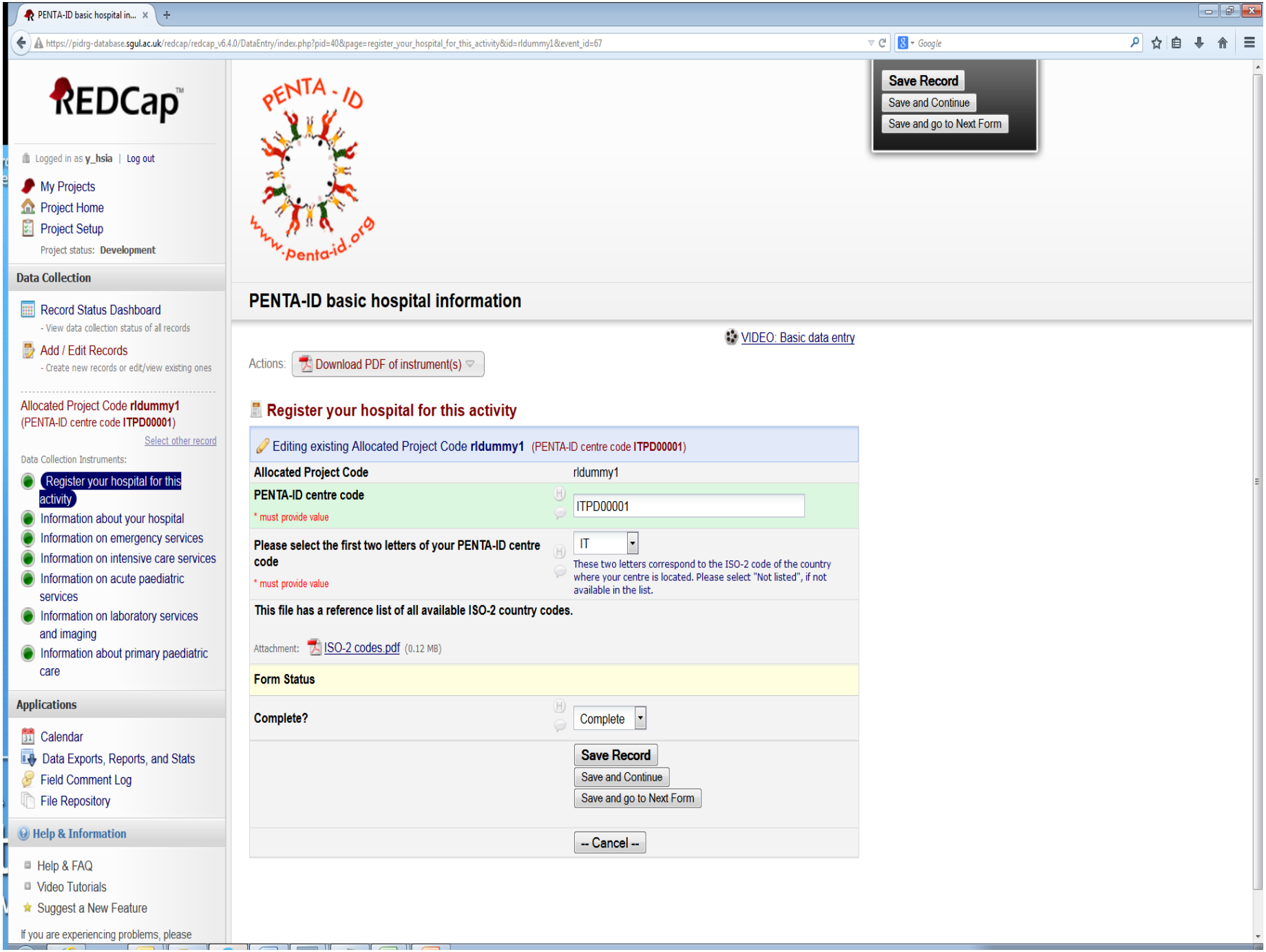
Antifungal	PIP	COMPLETION			
Amphotericin B	NO	n.a.			
Flucytosine	NO	n.a.			
Fluconazole	NO	n.a.			
Itraconazole	NO	n.a.			
Voriconazole	YES	May 2012			
Posaconazole	YES	By 2020			
Isavuconazole	YES	Dec 2019			
Micafungin	NO	n.a.			
Caspofungin	YES	Aug 2007			
Anidulafungin	YES	Oct 2013			

P-ID Ethics/Regulatory/PPI net

- High level of experience in ethics of conducting anti-infective trials in children
- Acute infections new issues – deferred consent
- Regulatory expertise
- PPI - PIDKids

P-ID data

- Opportunity to further develop PENTA-ID Clinical Network
- Core data set - annual basic centre data
- Each hospital/centre has P-ID number
- REDCap (Research Electronic Data Capture)
- Encouraged to recruit into range of studies
- Easier for centres – developing expertise and widen interests – encourage next generation


PENTA-ID basic hospital in...
https://pidrg-database.sgul.ac.uk/redcap/redcap_v6.4.0/DataEntry/index.php?pid=40&page=register_your_hospital_for_this_activity&id=rldummy1&event_id=67
REDCap
Logged in as y_hsia | Log out
My Projects
Project Home
Project Setup
Project status: Development
Data Collection
Record Status Dashboard
- View data collection status of all records
Add / Edit Records
- Create new records or edit/view existing ones
Allocated Project Code rldummy1
(PENTA-ID centre code ITPD00001)
Select other record
Data Collection Instruments:
Register your hospital for this activity
Information about your hospital
Information on emergency services
Information on intensive care services
Information on acute paediatric services
Information on laboratory services and imaging
Information about primary paediatric care
Applications
Calendar
Data Exports, Reports, and Stats
Field Comment Log
File Repository
Help & Information
Help & FAQ
Video Tutorials
Suggest a New Feature
If you are experiencing problems, please
PENTA - ID
www.penta-id.org
Save Record
Save and Continue
Save and go to Next Form
PENTA-ID basic hospital information
VIDEO: Basic data entry
Actions:
Download PDF of instrument(s)
Register your hospital for this activity
Editing existing Allocated Project Code rldummy1 (PENTA-ID centre code ITPD00001)
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These two letters correspond to the ISO-2 code of the country where your centre is located. Please select "Not listed", if not available in the list.
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P-ID Next steps?

- Build high quality observational cohort data in a wide range of clinical infection syndromes
- Develop hypotheses and data for investigator led studies
- Place P-ID in a strong position to conduct pharma led studies
- Build international collaboration
- Work with Enpr-EMA and other stake holders to optimise study design and conduct