



Optimising the treatment of *Enterococcus faecalis* endocarditis in Europe

AMPICEF: Montage d'un projet Européen

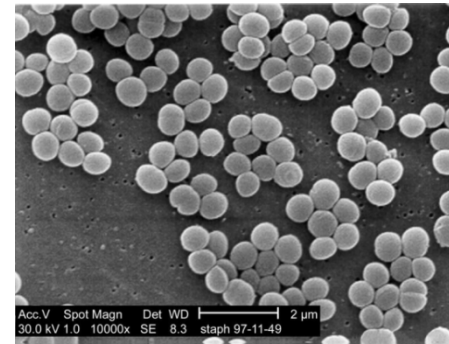
Pierre Tattevin, Jose Miro, Efthymia Giannitsioti, Riccardo Utili,
Jan van der Meer, Lars Olaison, Niels Eske-Bruun,
Emanuele Durante-Mangoni, Katarina Westling, Roland Leclercq,
Wouter Dreschler, Xavier Duval, Jordi Vila, Vincent Le Moing,
Carlos Mestres, Evangelis Giamarellos-Bourboulis, Bruno Hoen,

Partenaires : AEPEI, ICE

Endocardites à entérocoque

- 10% des endocardites infectieuses (EI)
 - 150 cas/an en France (EI 'certaine' selon Duke)
 - Dont 90% *Enterococcus faecalis*

(PHRC EI 2008)



- Âge moyen > 65 ans
- Co-morbidités multiples
- Recommandations traitement
 - Ampicilline ou amoxicilline + gentamicine
 - 4 à 6 semaines d'association

(recos européennes 2009)

La solution Suédoise

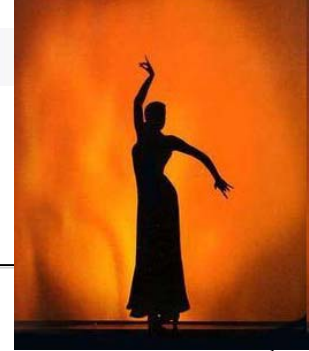


Reference, author	Year of study	No. of episodes	Cure, % ^a	Antibiotic therapy in cured episodes, median days	
				Cell wall active ^b	Aminoglycoside ^c
[5] Geraci and Martin	1954	14	50	38	38
[6] Vogler et al.	1962	13	77	—	—
[7] Mandell et al.	1970	36	83	42 ^d	42 ^d
[8] Moellering et al.	1974	14	57	36	24
[9] Wilson et al.	1984	56	88	28 ^d	28 ^d
[10] Rice et al.	1991 ^e	40	73	39 ^d	35 ^d
Present study	2002	93	81	42	15

^a Cure implies no death during treatment and no relapse at follow-up.

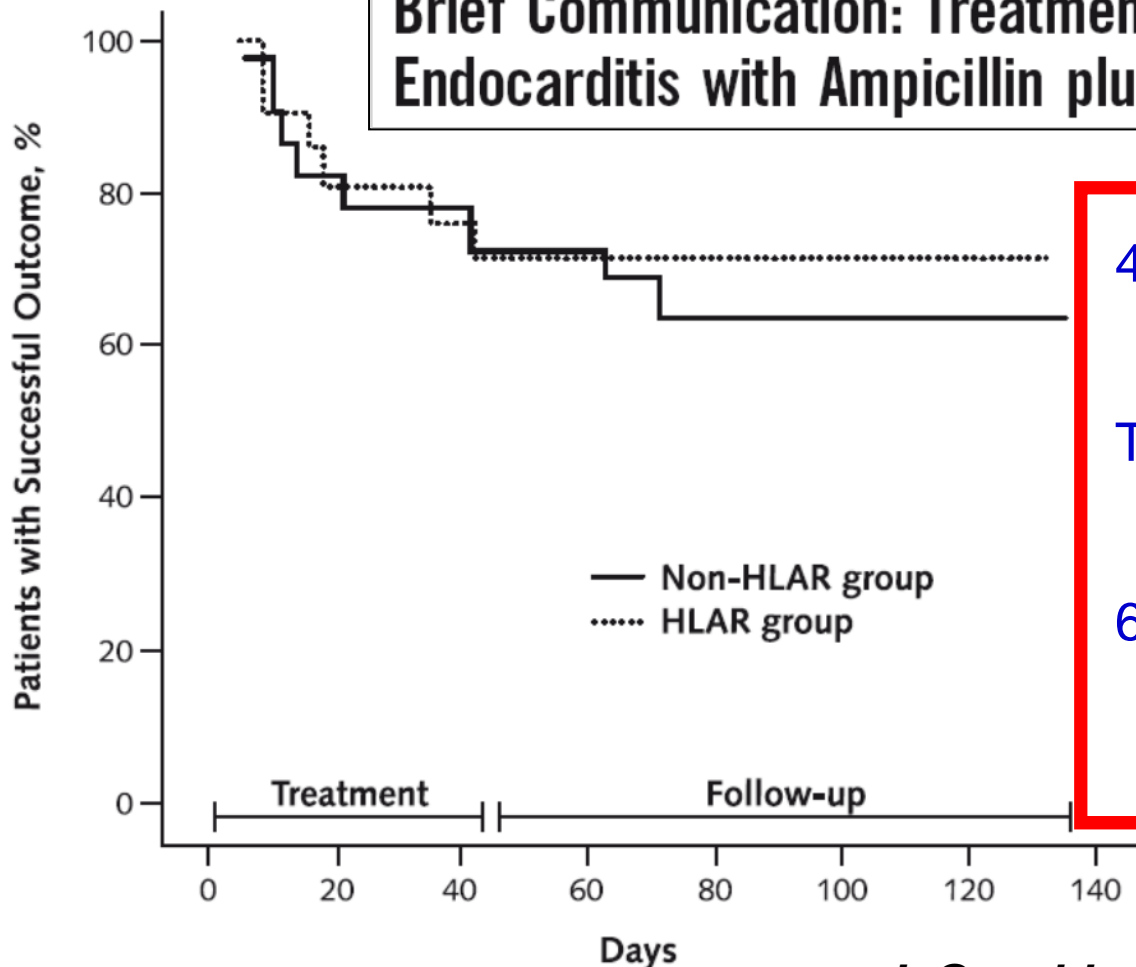
^b Cell wall-active agents implicates penicillin, ampicillin, or vancomycin.

La solution Espagnole



Annals of Internal Medicine

Brief Communication: Treatment of *Enterococcus faecalis* Endocarditis with Ampicillin plus Ceftriaxone



43 EI *Enterococcus faecalis*

- 21 HNR gentamicine
- 22 BNR

Traitement 6 semaines

- ampicilline 2 g x 6/j
- ceftriaxone 2 g x 2/j

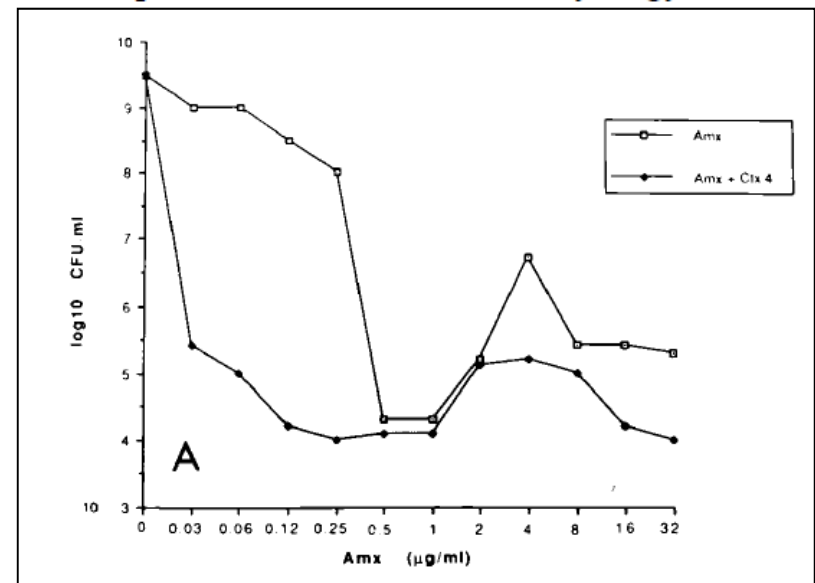
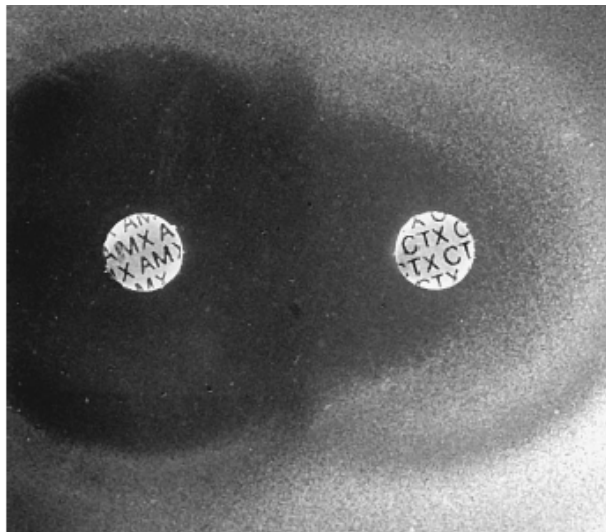
67% guérison à 3 mois

- Un seul échec microbio (EI sur prothèse valve aortique + Dacron aorte)

Synergistic Effect of Amoxicillin and Cefotaxime against *Enterococcus faecalis*

JEAN-LUC MAINARDI,^{1*} LAURENT GUTMANN,² JACQUES F. ACAR,^{1,2} AND FRED W. GOLDSTEIN¹

The Minimal Inhibitory Concentration (MIC) of amoxicillin that inhibited 50% of isolates decreased from 0.5 to 0.06 mg/L in the presence of only 4 mg/L of cefotaxime. Alternatively, the MIC of cefotaxime that inhibited 50% of isolates decreased from 256 to 1 mg/L in the presence of only 0.06 mg/L of amoxicillin. By using a penicillin-binding protein (PBP) competition assay, the authors suggested that the partial saturation of PBPs 4 and 5 by amoxicillin combined with the total saturation of PBPs 2 and 3 by cefotaxime could be responsible for the observed synergy between these two compounds [22].



La solution Française ?



■ Pour l'instant

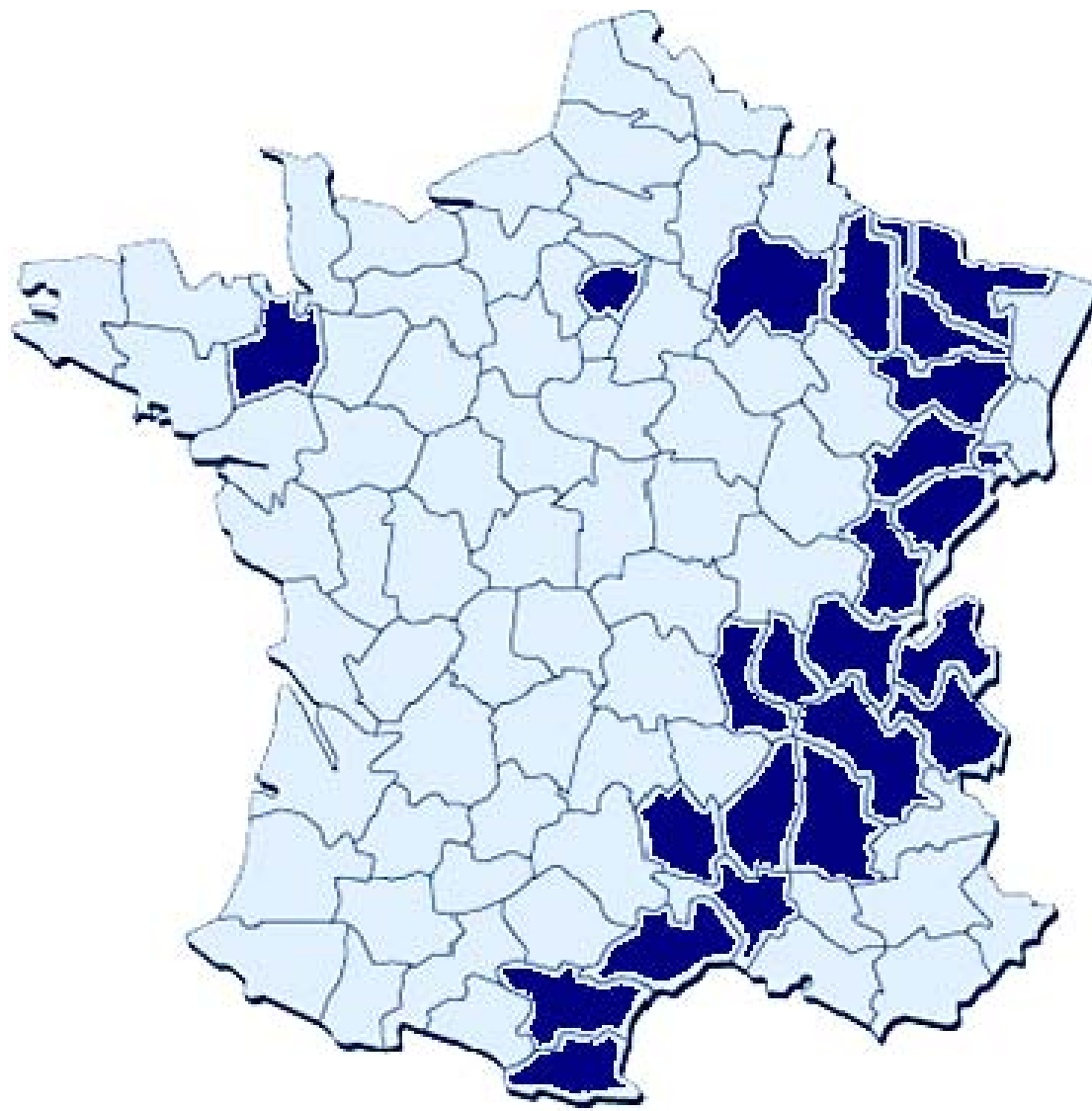
- Officiellement, recommandations européennes
- Prescriptions gentamicine : quelques libertés...
 - Durée 2 à 6 semaines
 - Modalités : 1/j de préférence – monitoring résiduelles
 - **39% des infectiologues français suivent les recos**
(*G. Beraud et al. Poster K-2174, Tuesday, ICAAC 2010*)
- Mortalité hospitalière 20%
- Chirurgie 50%

Projet PHRC national 2010

- **Etude randomisée, ouverte, de non-infériorité**
 - Amoxicilline-gentamicine
 - Amoxicilline-ceftriaxone
- **Critère principal composite 'évolution favorable'**
 - Survie sans séquelles significatives
 - Guérison (hémocultures 'test-of-cure' = S12)
- **Nb de patients nécessaires (β 20%, α 5%, +/- 15%)**
 - Étude de non-infériorité -> 130 patients évaluable par bras
 - Durée 3 ans
 - OK si inclusion 30% des EI françaises à *E. faecalis*...

Principal défi = Le recrutement

- Départements participant aux études de l'AEPEI



HEALTH.2011.2.3.1-1

Investigator-driven clinical trials of off-patent antibiotics.

FP7- HEALTH-2011-two-stage.

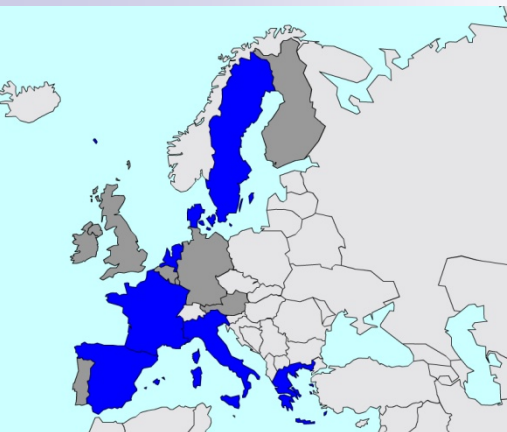
Calendrier

Publication of call	<i>20 July 2010</i>
Deadline for submission of stage one proposals	<i>13 October 2010, 17:00:00 Brussels time</i>
Evaluation of stage one proposals	<i>Finalised by 3 December 2010</i>
Letter to coordinators of successful stage one proposals; invitation to submit a full stage two proposal	<i>By 10 December 2010</i>
Coordinators informed of results of first stage evaluation – stage one proposals	<i>By end-December 2010</i>
Deadline for submission of stage two proposals	<i>10 February 2011 17:00:00 Brussels time</i>

7^{ème} programme-cadre européen 'santé': Règles du jeu

- Max = 6 M € / projet
- Sont 'encouragés' (= obligatoires ?)
 - Consortium
 - Prise en charge globale (études ancillaires)
 - Dissémination du savoir (planifiée)
 - Standardisation des pratiques
 - Implication organisations patients
 - Participation PME 'à forte activité recherche'
- Débuts du FP-7 dans le domaine 'essais cliniques'
 - Alternative essais 'de firme'

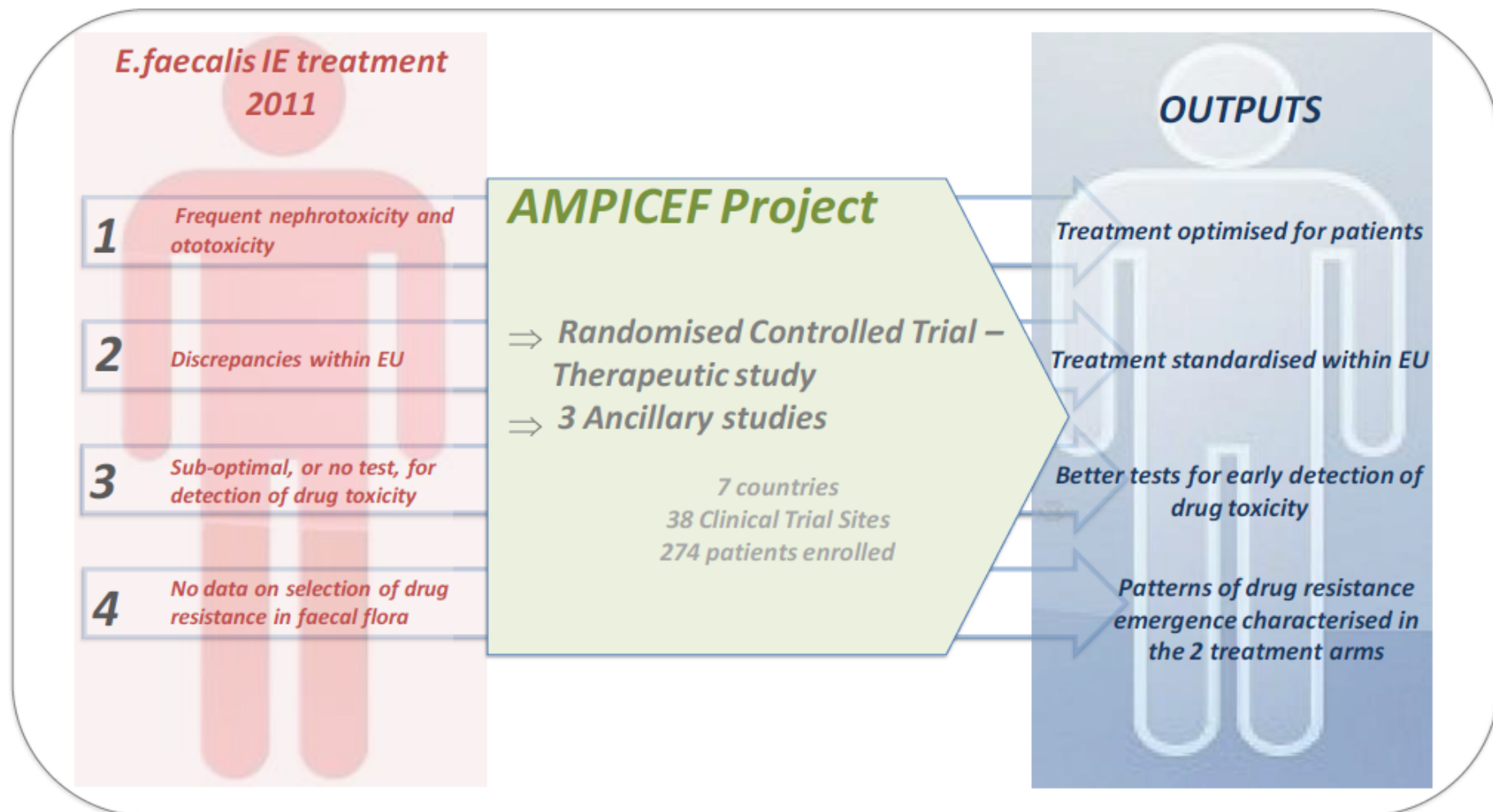
=> Peu (ou pas) de règles spécifiques (cf. protocole)



AMPICEF: Ampicillin-ceftriaxone vs. ampicillin-gentamicin for the treatment of *Enterococcus faecalis* endocarditis: An international, randomized, open-label study

**Pierre Tattevin, Jose Miro, Efthymia Giannitsioti, Riccardo Utili,
Jan van der Meer, Lars Olaison, Niels Eske-Bruun,
Emanuele Durante-Mangoni, Katarina Westling, Roland Leclercq,
Wouter Dreschler, Xavier Duval, Jordi Vila, Vincent Le Moing,
Carlos Mestres, Evangelis Giamarellos-Bourboulis, Bruno Hoen,
for the AMPICEF consortium**

Figure 1.1.a. AMPICEF Overall concept



PATIENTS

Diagnosis of E. faecalis endocarditis

Randomisation

TREATMENTS

1

2

RESULTS

Efficacy

1

=

Efficacy

2

Tolerability

1

>

Tolerability

2

1

Combination ampicillin-ceftriaxone

2

Combination ampicillin-gentamicin

Ancillary studies

- Impact of ampi/ceftriaxone vs ampi/gentamicin
 - on fecal flora (ESBL, *Clostridium difficile*, MRSA)
 - on microbiome ?
- Enterococcus isolates testings
 - virulence, molecular epidemiology
 - Susceptibility *in vitro*
- New imaging for digestive investigations
 - Videocapsules vs endoscopy
- Hearing loss
 - Speech-in-noise testing through cell phones
- Risk of enterococcus IE and thrombophilic conditions
- Hemorrhagic events with high doses betalactams

Suggested ancillary studies

- Impact of ampi/ceftriaxone vs ampi/gentamicin
 - on fecal flora (ESBL, *Clostridium difficile*, MRSA)
 - on microbiome ?
- Enterococcus isolates testings
 - virulence, molecular epidemiology
 - Susceptibility *in vitro*

**Work package
'microbiology'**

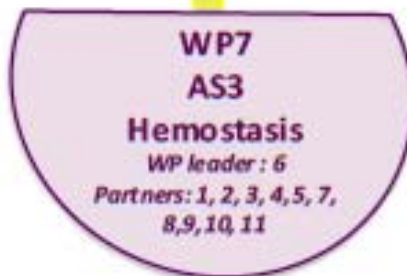
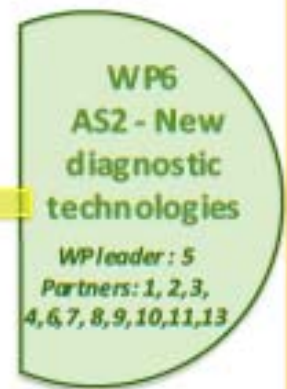
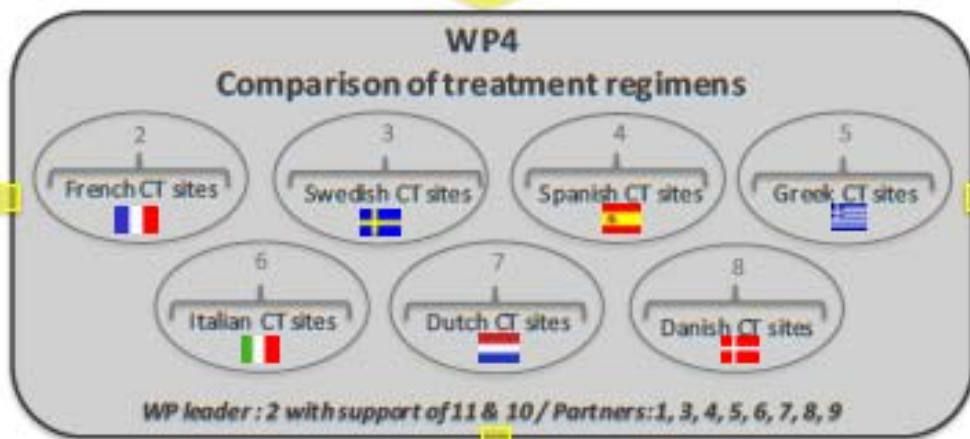
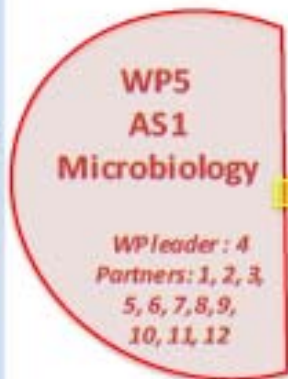
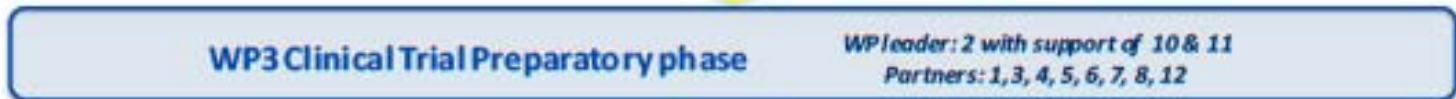
- New imaging for digestive investigations
 - Videocapsules vs endoscopy
- Hearing loss
 - Speech-in-noise testing through cell phones

**Work package
'new technology'**

- Risk of enterococcus IE and thrombophilic conditions
- Hemorrhagic events with high doses BL

**Work package
'hemostasis'**

Project chart



WP leader: 1

WP1 - Management

WP leader: 9

Partners: 1, 3, 4, 5, 6, 7, 8, 10

WP8 Dissemination

Figure 2.4.b. EC AMPICEF Budget breakdown per partner and per type of activities

	RTD or related		Dissemination		Management		Total	
	Costs	Requested grant to the budget (CE)	Costs	Requested grant to the budget (CE)	Costs	Requested grant to the budget (CE)	Costs	Requested grant to the budget
P1 - UR1	86 400	64 800	142 400	142 400	374 480	374 480	603 280	581 680
P2 - CHURENNES	358 868	269 151	0	0	0	0	358 868	269 151
P3 - UGOT	651 179	488 384	0	0	4 000	4 000	655 179	492 384
P4 - FCRB	1 240 350	930 263	0	0	6 000	6 000	1 246 350	936 263
P5 - NKUA	594 000	445 500	0	0	0	0	594 000	445 500
P6 - SUN	577 200	432 900	0	0	7 000	7 000	584 200	439 900
P7 - AMC	841 037	630 778	0	0	0	0	841 037	630 778
P8 - REGIONH	320 416	240 312	0	0	0	0	320 416	240 312
P9 - CHRUB	47 144	35 358	100 352	100 352	0	0	147 496	135 710
P10 - CHRUMTP	354 021	265 516	0	0	0	0	354 021	265 516
P11 - PIERREL	1 615 050	1 211 288	0	0	10 000	10 000	1 625 050	1 221 288
P12 - UNICAEN	265 397	199 048	0	0	0	0	265 397	199 048
P13 - ARGUTUS	179 400	134 550	0	0	0	0	179 400	134 550
TOTAL	7 130 462	5 347 847	242 752	242 752	401 480	401 480	7 774 694	5 992 079

Conclusions (1)

- Expérience prenante mais très enrichissante
 - CE pas habituée à financer des essais cliniques, *mais volonté politique affichée (alternative aux big pharma)*
 - Consolider un consortium international (ICE)
 - 1er essai randomisé dans l'EI depuis 20 ans !
- Soutien du département Europe de l'Université Rennes-I (Bretagne-Valorisation)
 - Alice Ruczinski & Julien Lefeuvre
 - Financement régional (dispositif FP-7) = 30 k€
 - Réunion de tous les partenaires à Rennes



Conclusions (2)

■ Résultats

- 770 projets 'santé' soumis à la 1ère étape
- 220 sélectionnés pour la 2ème étape (dont nous !)
- 95 finalement retenus (dont nous + 3 autres 'français')
- Seuls 91 sont assurés d'être financés (pas nous...)

■ Enjeu majeur

- Réactiver les essais randomisés pour l'EI (mieux que les lapins, ou le 'copié-collé' des recos précédentes...)
- Batir un consortium pour études ultérieures



Opportunités infectieux FP7-2012

ORIENTATION PAPER

Proposed priorities for innovative health research 2012

Working document – not legally binding

Indicative publication date for all documents including the final work programme is 20 July 2011. All related documents will then be accessible via
<http://cordis.europa.eu/fp7/dc/index.cfm>

2.3 Translational research in major infectious diseases: to confront major threats to public health

2.3.1 Anti-microbial drug resistance.....

Closed in 2012.....

2.3.2 HIV/AIDS, malaria and tuberculosis.....

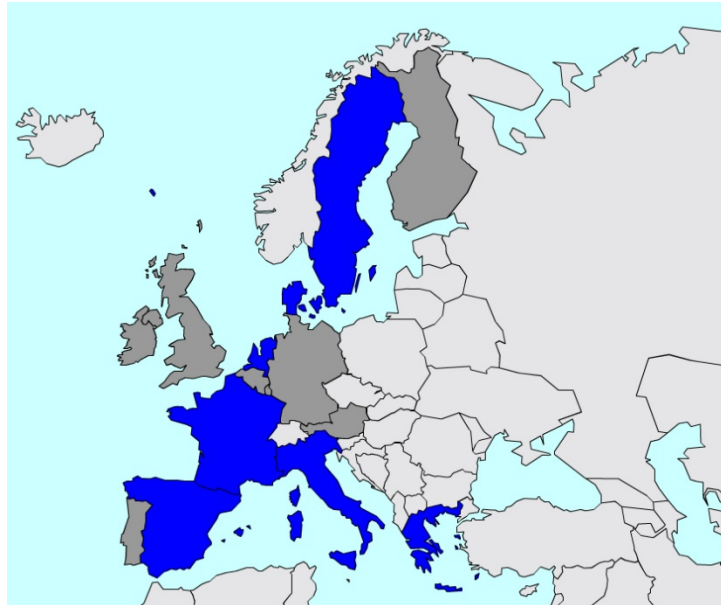
2.3.3 Potentially new and re-emerging epidemics.....

Closed in 2012.....

2.3.4 Neglected infectious diseases.....

Closed in 2012.....

The AMPICEF consortium



Pierre Tattevin, Jose Miro, Efthymia Giannitsioti, Riccardo Utili, Jan van der Meer, Lars Olaison, Niels Eske-Bruun, Emanuele Durante-Mangoni, Katarina Westling, Roland Leclercq, Wouter Dreschler, Xavier Duval, Jordi Vila, Vincent Le Moing, Carlos Mestres, Evangelis Giamarellos-Bourboulis, Bruno Hoen



Support for EU research project: Alice Ruczinski & Julien Lefeuvre