Antimicrobial prophylaxis in IE:
What is the evidence? What are the guidelines?

Bruno Hoen

University of Lorraine Medical Center at Nancy

- “There is ***no proof*** that prophylaxis with antibiotics is effective in persons…undergoing procedures associated with transient bacteremia.
- However, the use of prophylactic antibiotics appears to be a reasonable approach to the problem and the ***consensus of opinion*** strongly supports the use of antibiotics in this situation”

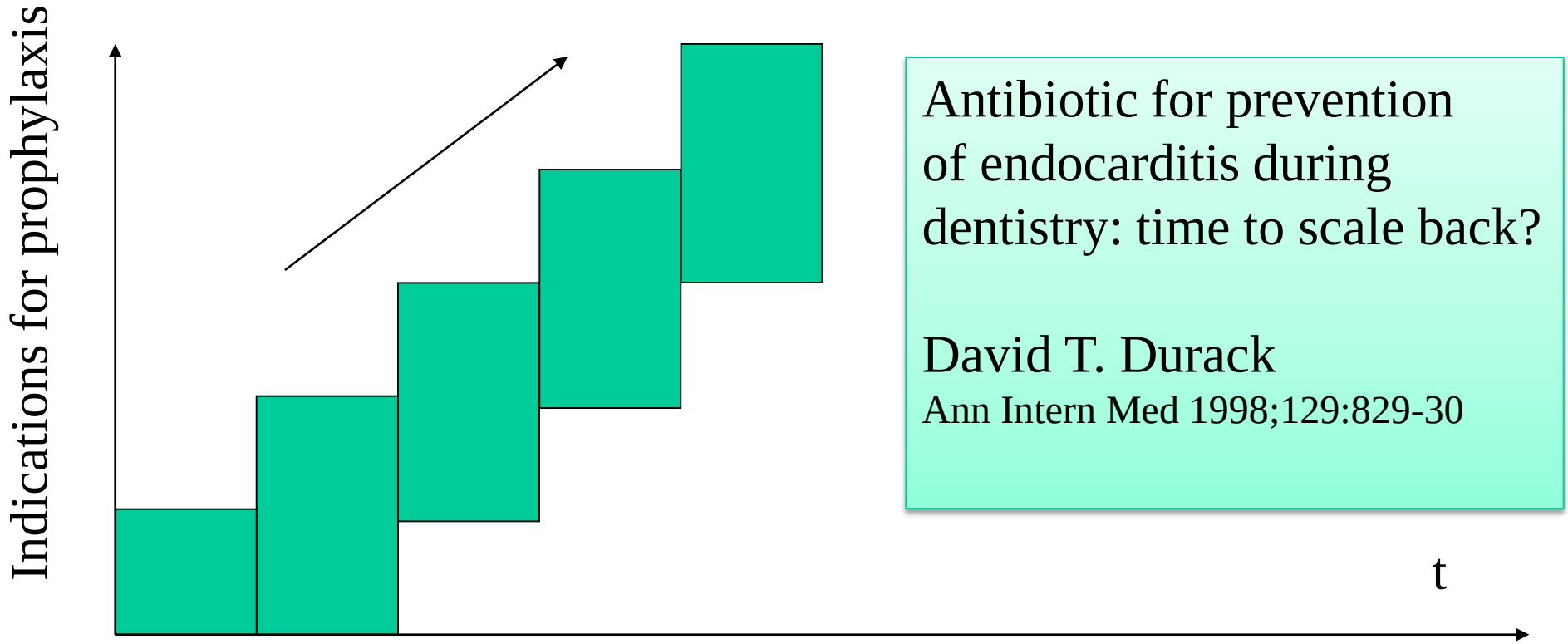
Hook and Kaye, 1962

Expert guidelines & consensus conferences

- USA (AHA):
  - 1954, 1965, 1977, 1984, 1990, 1997, 2007, 2014
- GB :
  - 1982, 1986, 1990, 1992, 2006 (BSAC)
  - 2008 (NICE)
- Switzerland
  - 1984, 2000
- France (SPILF/AEPEI)
  - 1992, 2002
- Europe (ESC/ESCMID)
  - 2004, 2009, 2015

Existing guidelines for IE prophylaxis in 2002

The number of procedures for which antibiotic prophylaxis was recommended had steadily increased over the past decades



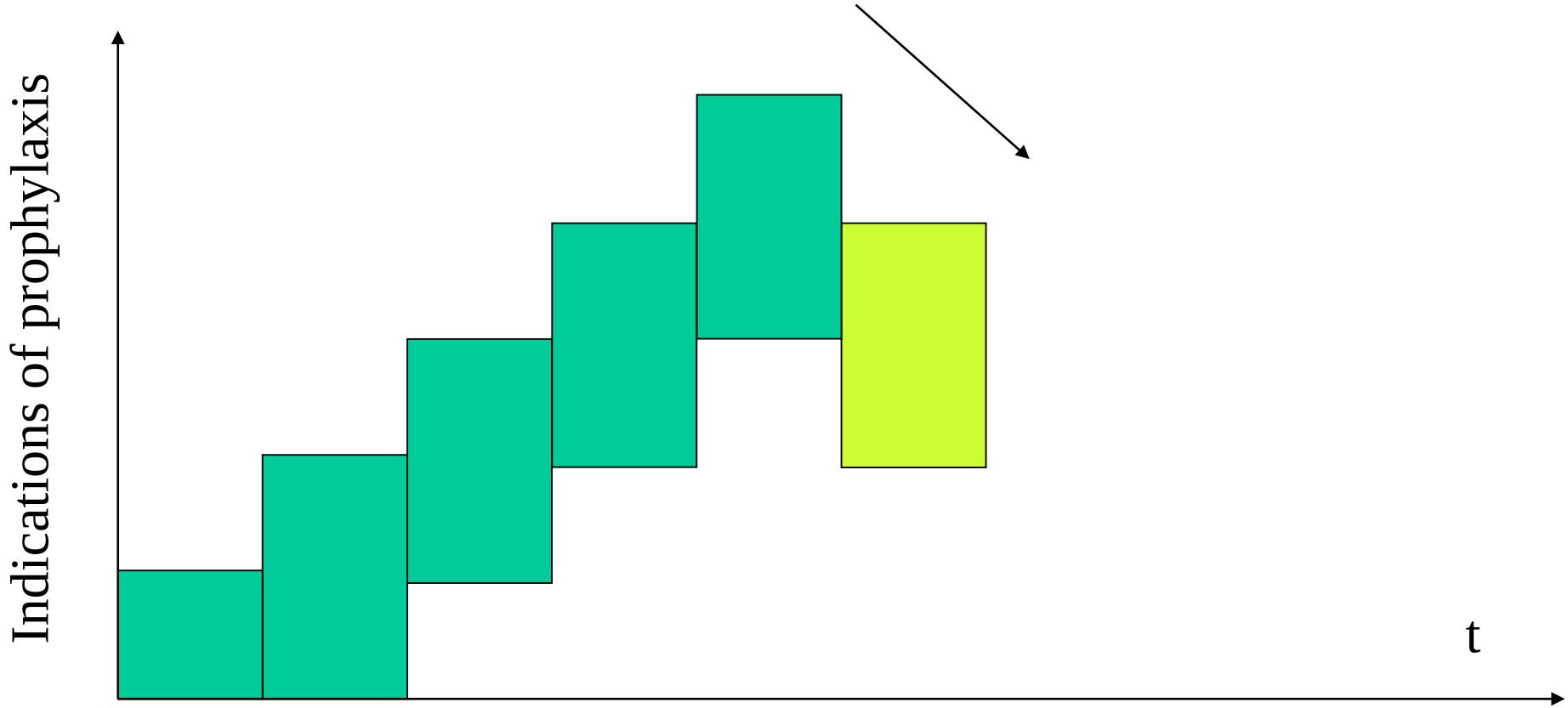
Antibiotic for prevention of endocarditis during dentistry: time to scale back?

David T. Durack

Ann Intern Med 1998;129:829-30

French 2002 guidelines

First step back in IE prophylaxis indications



ELSEVIER

Médecine et maladies infectieuses

www.elsevier.com/locate/medmal

Short text*

Prophylaxis of infective endocarditis

Revision of the march 1992 French consensus conference

French Recommendations 2002

Médecine et maladies infectieuses 2002;32: 551-586

Heart ONLINE

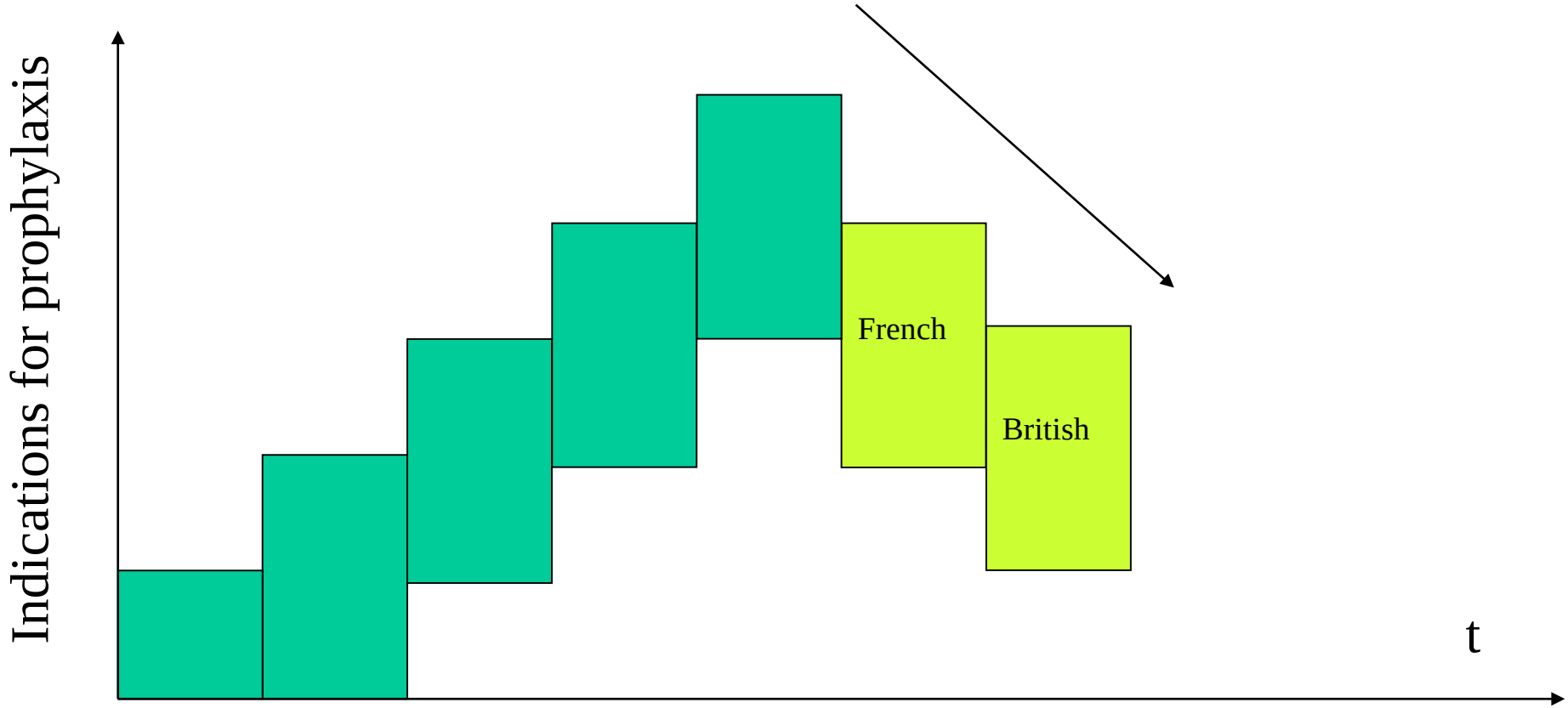
Prophylaxis of infective endocarditis: French recommendations 2002

N Danchin, X Duval and C Leport

Heart 2005;91;715-718
doi:10.1136/hrt.2003.033183

April 2006: British guidelines

Second step back in IE prophylaxis indications



Journal of Antimicrobial Chemotherapy (2006) **57**, 1035–1042
doi:10.1093/jac/dkl121
Advance Access publication 19 April 2006

JAC

Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy

F. K. Gould[1]*, T. S. J. Elliott[2], J. Foweraker[3], M. Fulford[4], J. D. Perry[1], G. J. Roberts[5], J. A. T. Sandoe[6] and R. W. Watkin[7]

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High-risk cardiac factors requiring antibiotic prophylaxis

Previous infective endocarditis

Cardiac valve replacement surgery, i.e. mechanical or biological prosthetic valves

Surgically constructed systemic or pulmonary shunt or conduit

Dental procedures requiring antibiotic prophylaxis

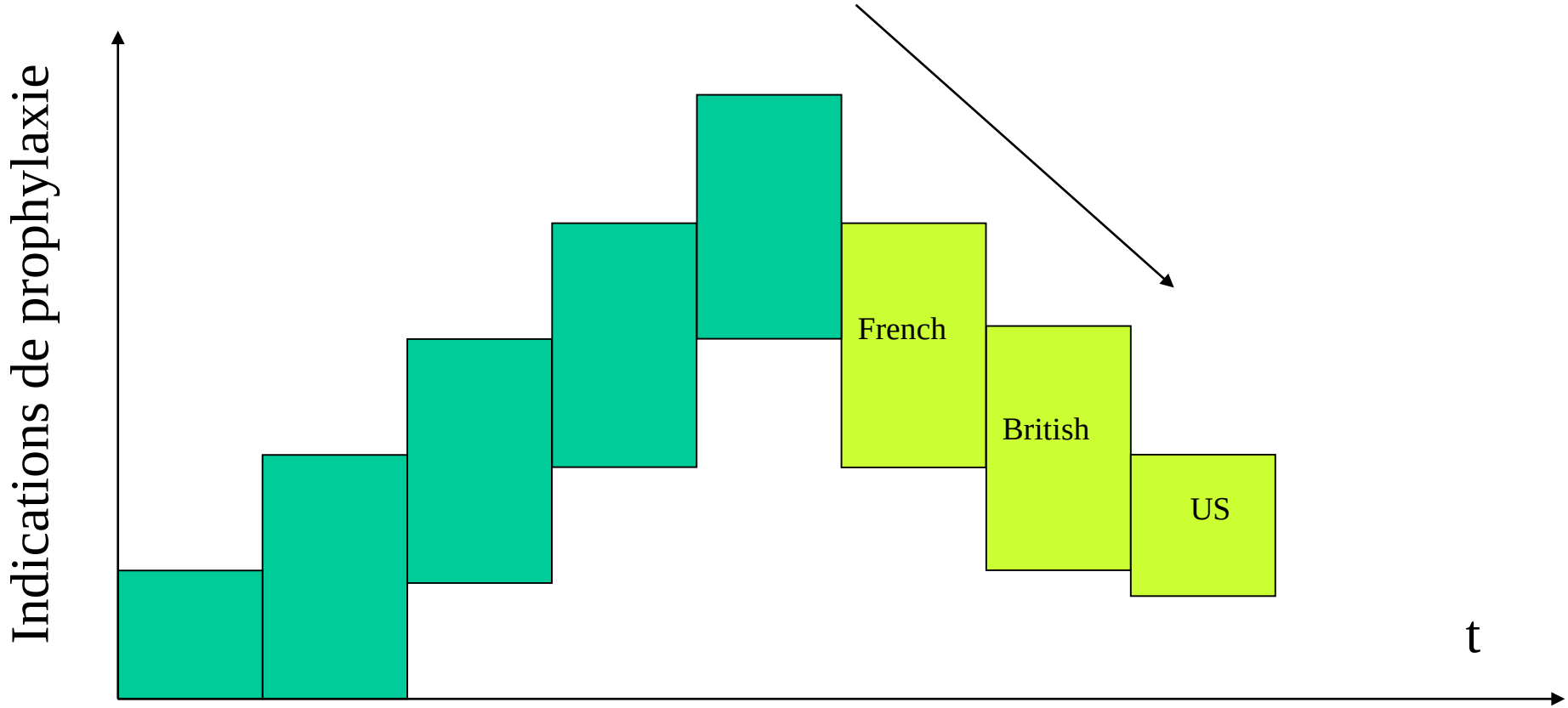
All dental procedures involving dento-gingival manipulation

BSAC guidelines 2006

Procedures	Anecdotally associated with endocarditis?	% Bacteraemia	Requires IE prophylaxis?
Oesophageal varices–sclerotherapy	yes[21,22]	10–50[23,24]	yes
Oesophageal stricture dilatation	yes[25]	21–54[23,26–29]	yes
Oesophageal varices–Banding	no	6[23]	no*
Oesophageal laser therapy	no	35[23]	yes
Endoscopy–upper	yes[30–33]	4[23]	no*
Sigmoidoscopy/colonoscopy	yes[34–37]	0–9[23,26,38]	no*
ERCP	no[39]	6–11[23]	yes
Percutaneous endoscopic gastrostomy	no	0[40]	no*
Echocardiography–transoesophageal	yes[41]	1–13[42,43]	no*

Avril 2007: US guidelines

Troisième étape dans la réduction de la prophylaxie



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association®
Learn and Live℠

Prevention of Infective Endocarditis. Guidelines From the American Heart Association. A Guideline From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group

Walter Wilson, Kathryn A. Taubert, Michael Gewitz, Peter B. Lockhart, Larry M. Baddour, Matthew Levison, Ann Bolger, Christopher H. Cabell, Masato Takahashi, Robert S. Baltimore, Jane W. Newburger, Brian L. Strom, Lloyd Y. Tani, Michael Gerber, Robert O. Bonow, Thomas Pallasch, Stanford T. Shulman, Anne H. Rowley, Jane C. Burns, Patricia Ferrieri, Timothy Gardner, David Goff and David T. Durack

Circulation published online Apr 19, 2007;

TABLE 2. Primary Reasons for Revision of the IE Prophylaxis Guidelines

IE is much more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, GI tract, or GU tract procedure.
Prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, GI tract, or GU tract procedure.
The risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy.
Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE.

Prevention of IE: Guidelines from the AHA

Cardiac conditions associated with the highest risk of adverse outcome from IE for which prophylaxis with dental procedures is recommended

- Prosthetic cardiac valve
- Previous IE
- Congenital heart disease (CHD)*
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

Wilson W, Circulation. 2007

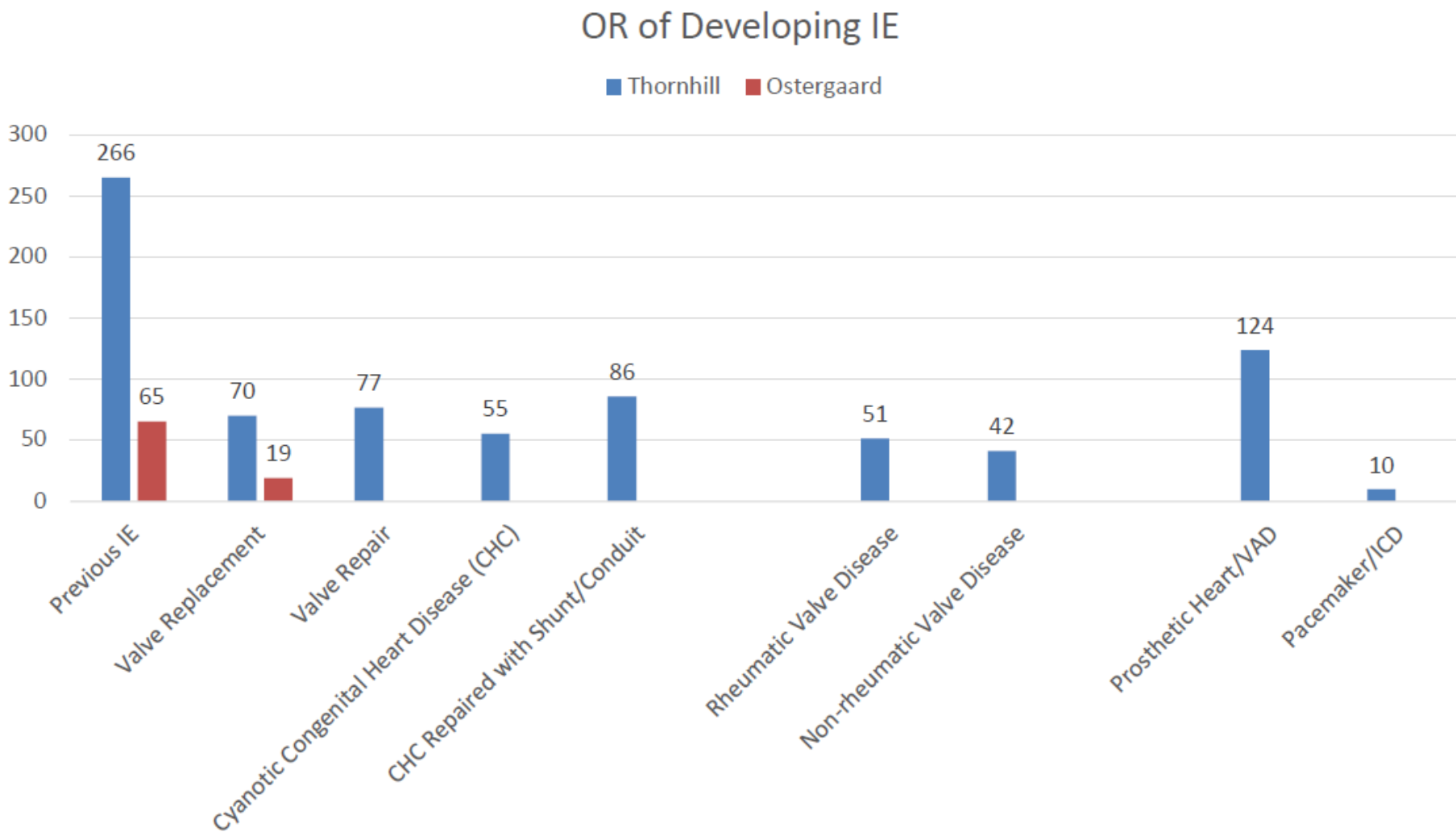
Prevention of IE: Guidelines from the AHA

- Limit recommendations for IE prophylaxis only to those conditions associated with the highest risk of adverse outcome from IE
- Antibiotic prophylaxis is recommended for all invasive dental procedures
- Antibiotic prophylaxis is recommended for procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissue
- Antibiotic prophylaxis solely to prevent IE is not recommended for GU or GI tract procedures

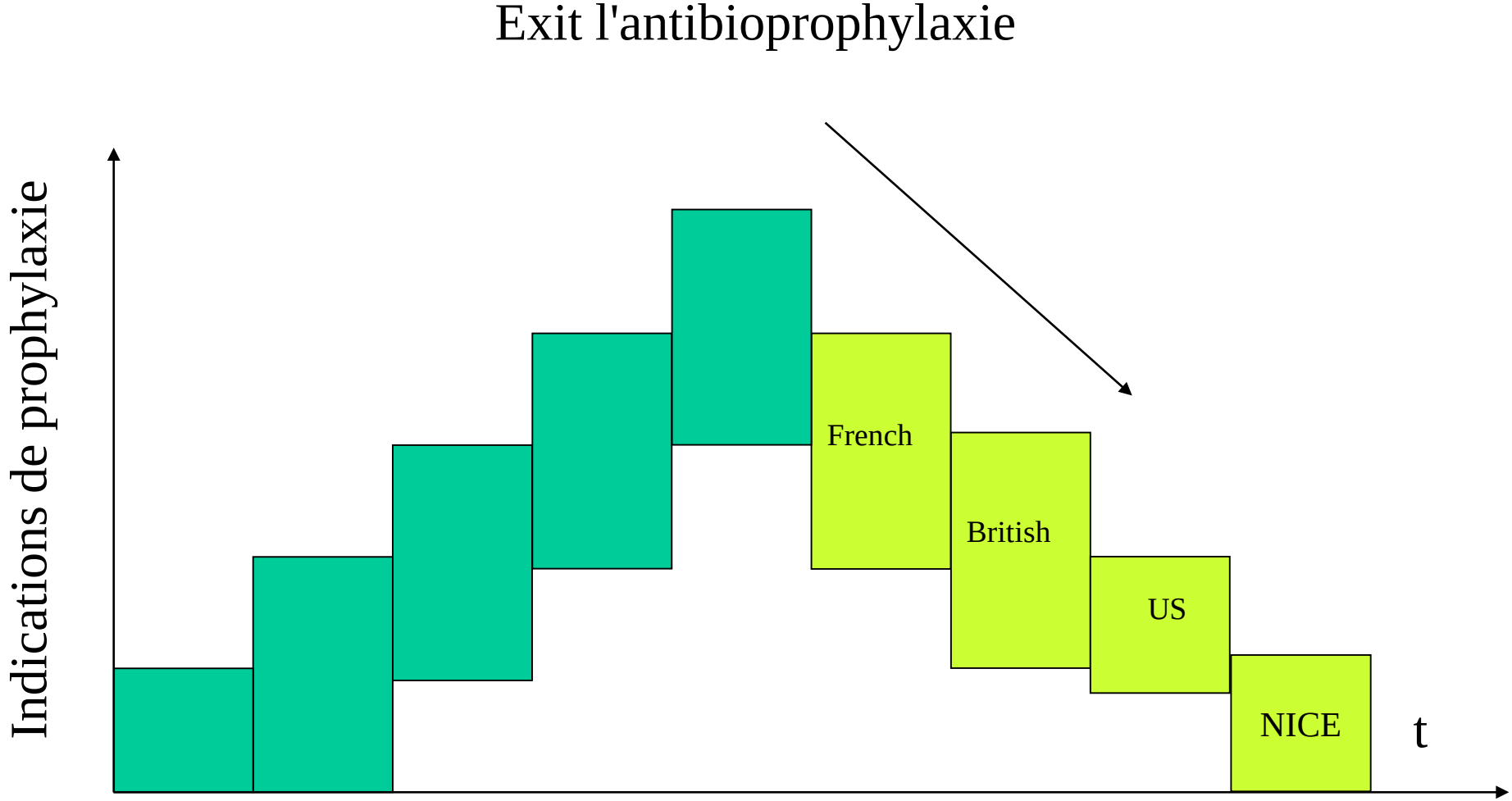
Wilson W, Circulation 2007

Thornhill et al. 2018, Ostergaard et al. 2018

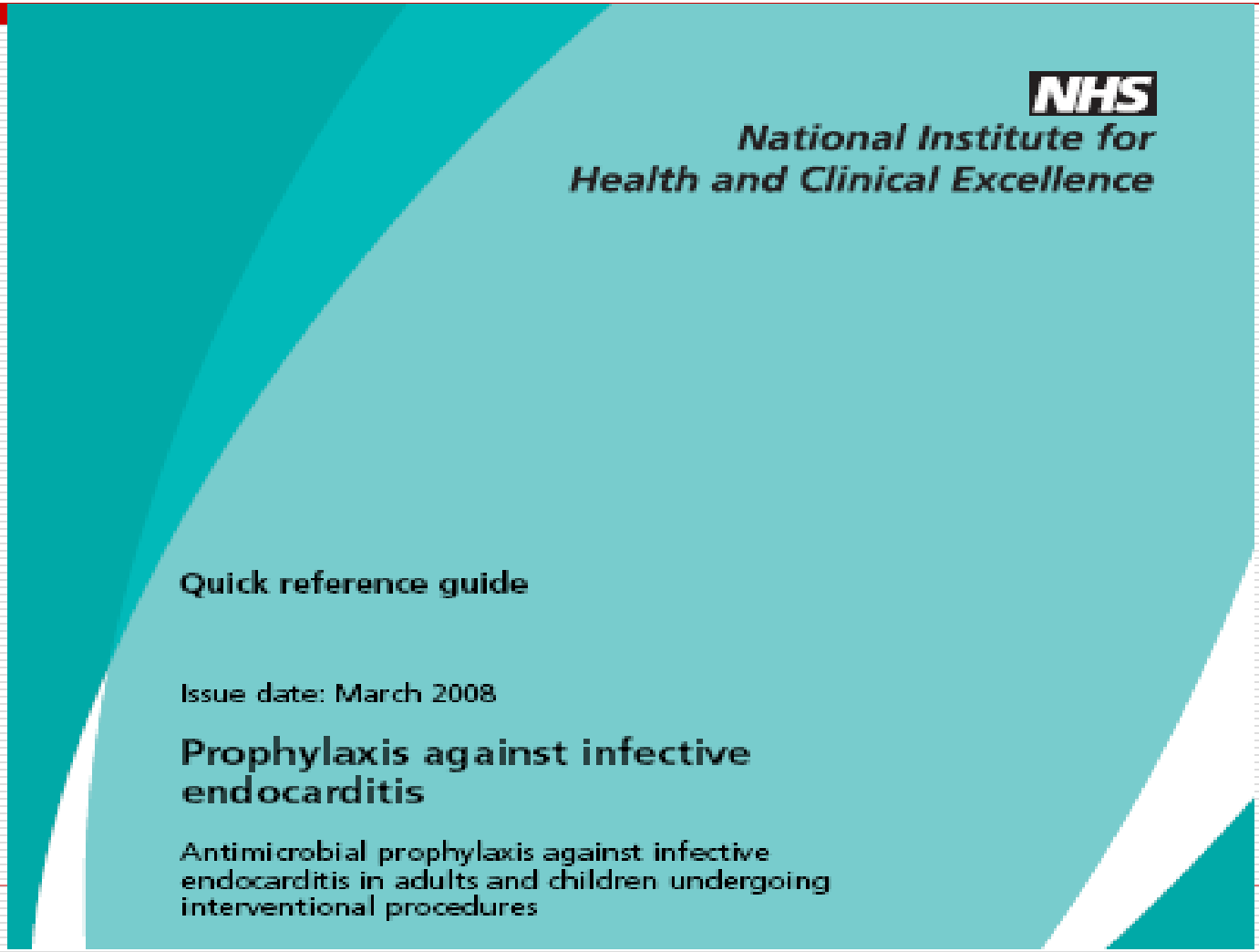
European Heart Journal, Volume 39, Issue 7, 14 February 2018, Pages 586–595, https://doi.org/10.1093/eurheartj/ehx655
European Heart Journal, Volume 39, Issue 7, 14 February 2018, Pages 623–629, https://doi.org/10.1093/eurheartj/ehx682



Mars 2008 : UK NICE clinical guideline



AP against IE is NOT RECOMMENDED!



www.nice.org.uk/CG064

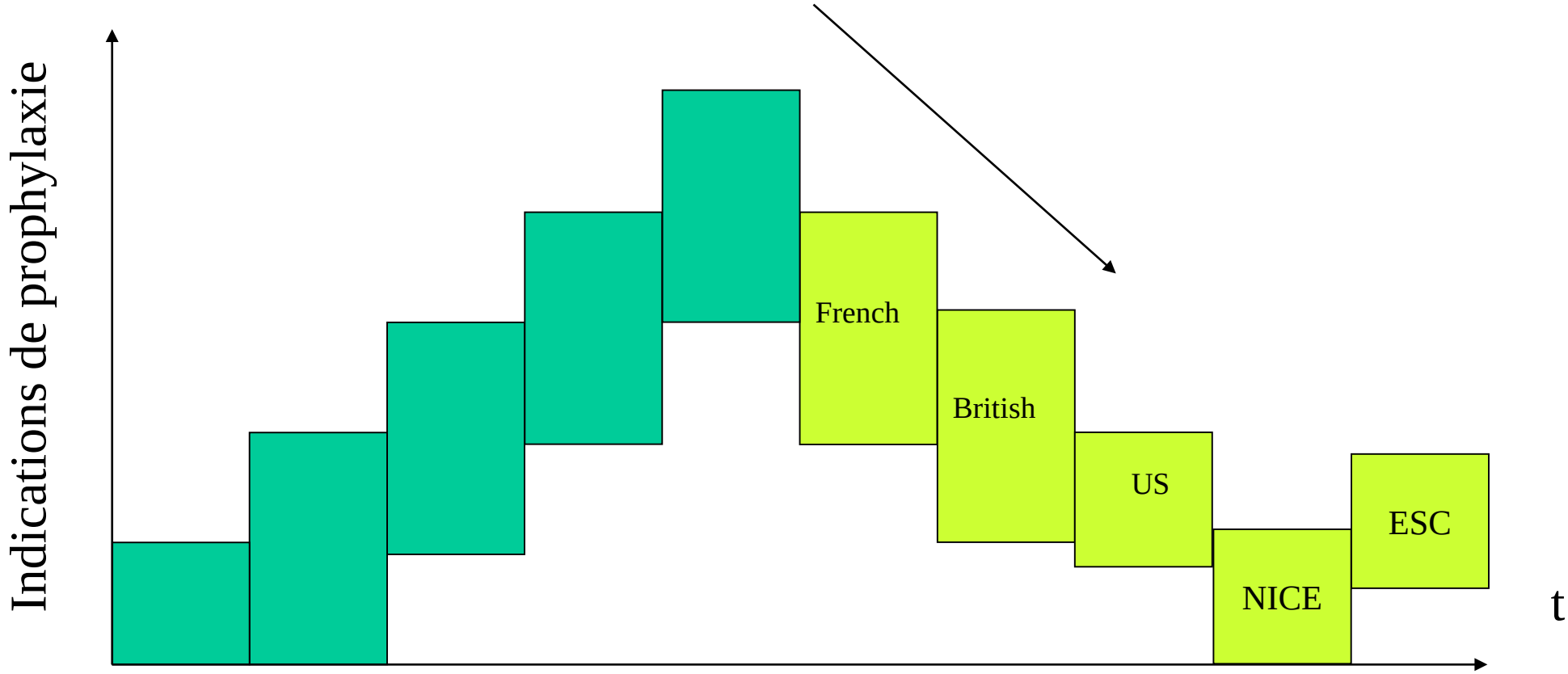
National Institute for Health and Clinical Excellence : prophylaxis against infective endocarditis

- Antibiotic prophylaxis against infective endocarditis is **NOT RECOMMENDED**
  - for people undergoing dental procedures
  - for people undergoing the following non-dental procedures:
    - upper and lower gastrointestinal tact
    - genitourinary tract ; this includes urological, gynaecological and obstretic procedures, and childbirth
    - upper and lower respiratory tract ; this includes ear, nose and throat procedures and bronchoscopy
- Chlorhexidine mouthwash should not be offered as prophylaxis against infective endocarditis undergoing dental procedures

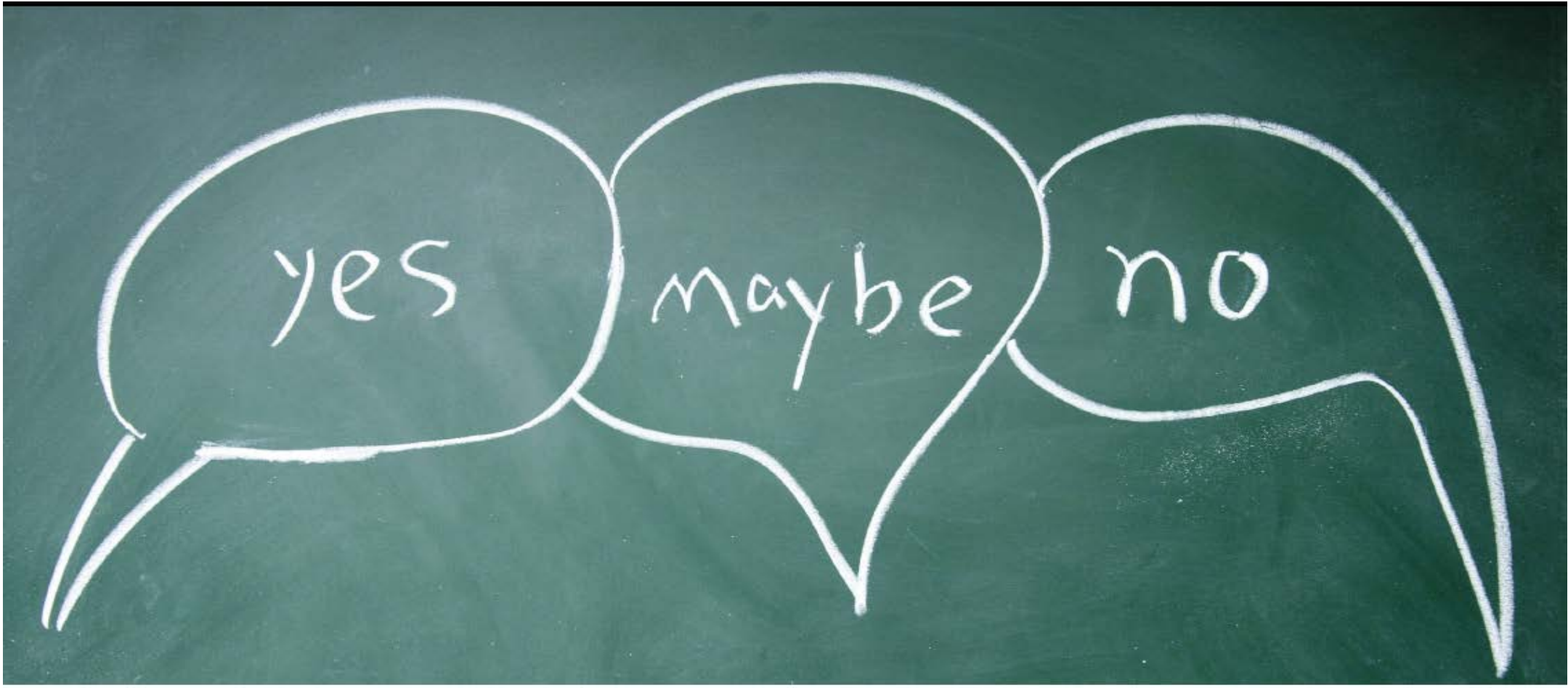
Nice clinical guidelines March 2008.

July 2009 : clinical guidelines ESC/ESCMID

It is not wise to give up antibiotic prophylaxis of IE



Confirmed en 2015



Controversy !

WHAT IS THE EVIDENCE FOR AP?

In Humans and Animals

Antibiotic prophylaxis of IE: summary of evidence

- Animal experimentations showed that AP effectively prevents IE
- Human experimental trials showed that penicillin prophylaxis reduces the incidence of bacteremia after dental extraction
- No RCT was ever conducted to confirm the efficacy and assess the benefit:risk ratio of AP
- Human observational studies
  - The efficacy of AP has been challenged in case-control studies
  - Transient bacteremia is common with normal daily activities such as tooth brushing, flossing and chewing food, which may contribute to the risk of IE at least as much as dental procedures
  - The widespread antibiotic use has been recognized to contribute to the emergence of antibiotic resistance
  - It is uncertain whether guideline changes had an impact on population incidence of IE
  - AP of IE has been –and still is– based on oral streptococcal IE models, while *S. aureus* has become the most frequent IE-causing pathogen

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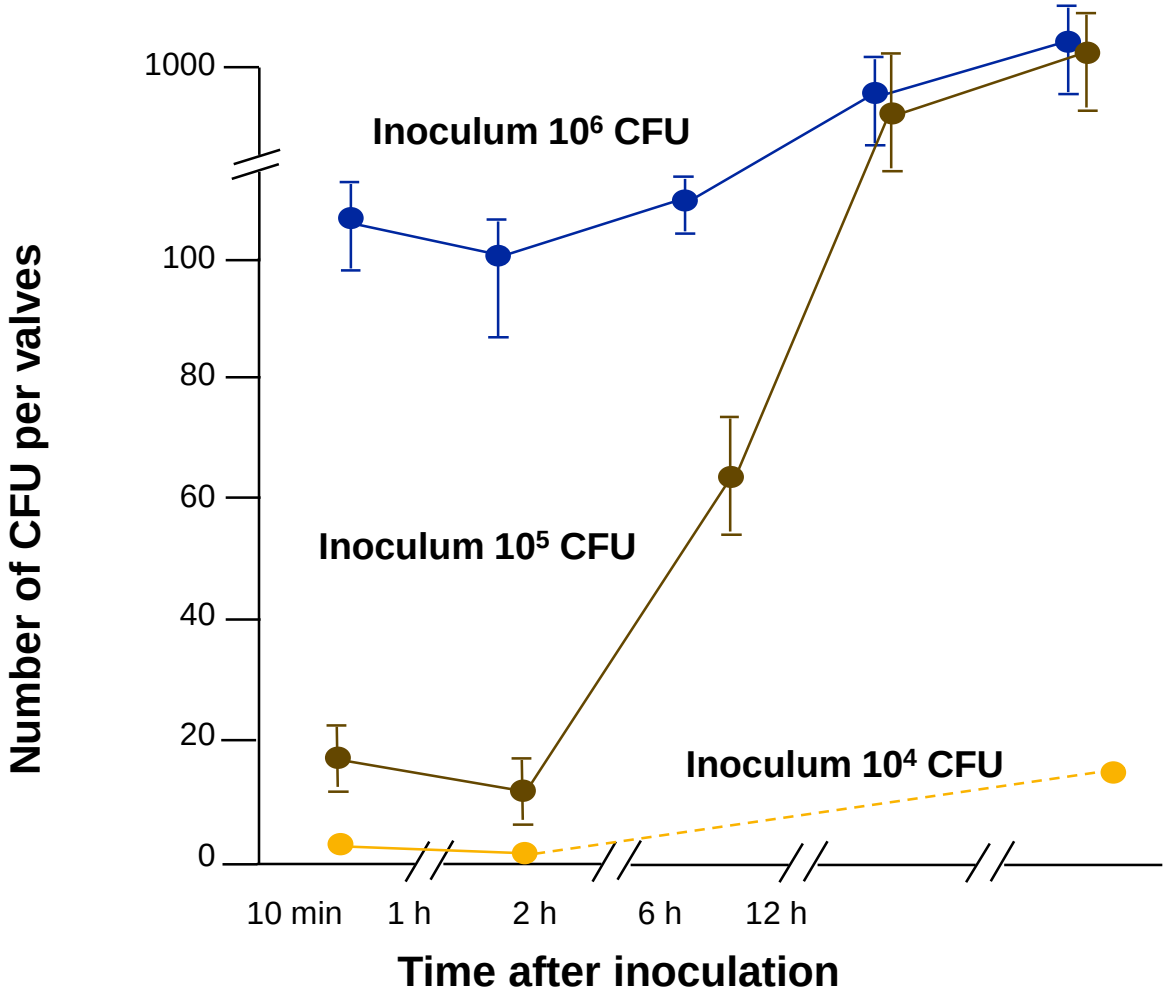
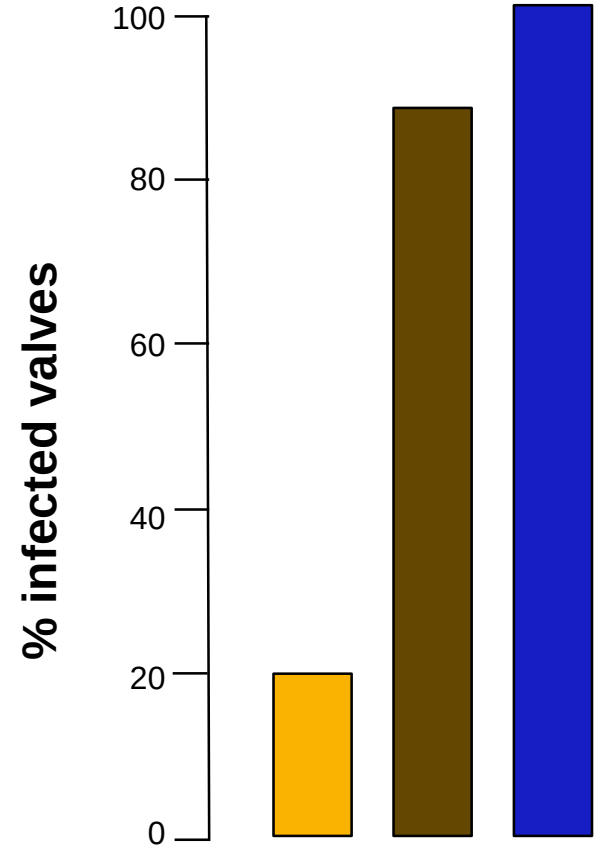
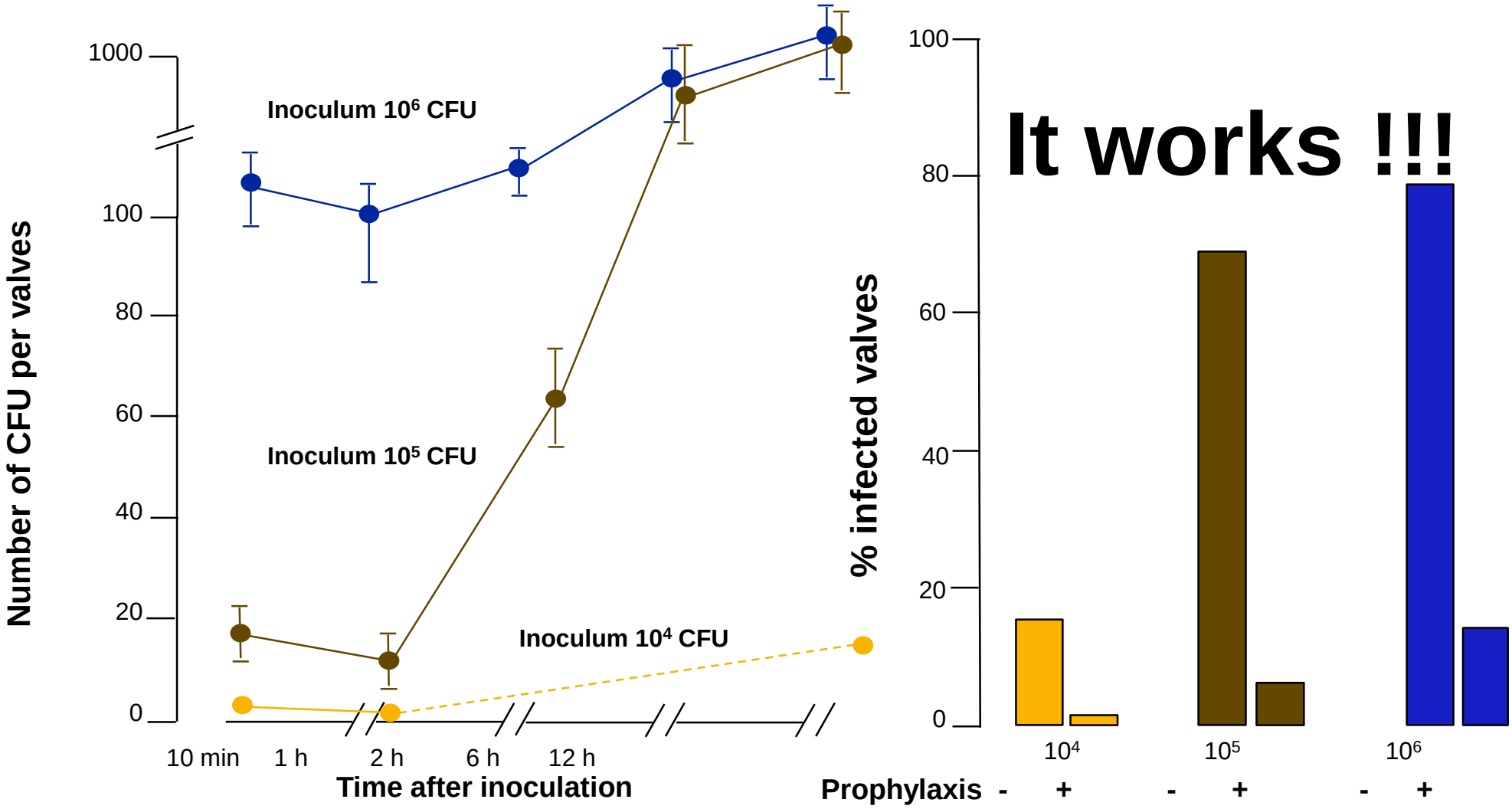
Effect of Bacterial Inoculum on Exp. IE Initiation





P Moreillon – UNI Lausanne

Single-dose Amoxicillin Prophylaxis in Streptococcal IE



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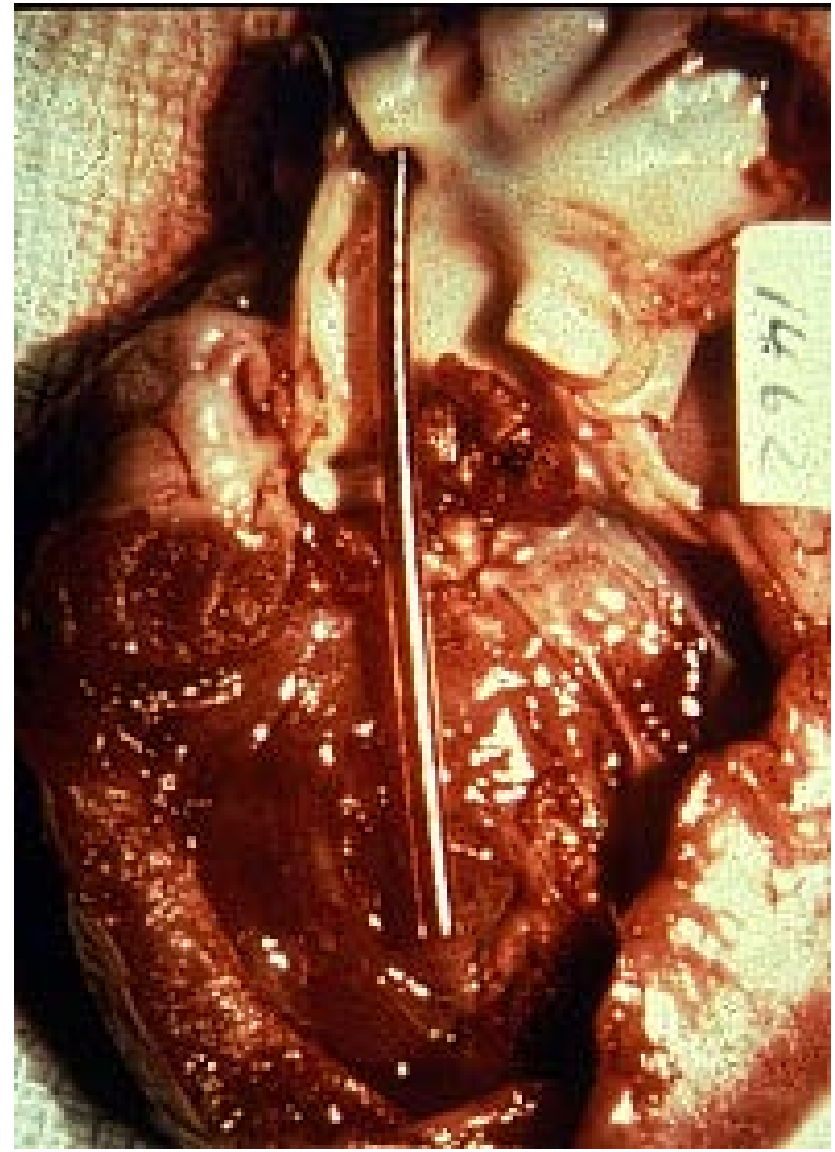
Experimental Endocarditis

- ***Inoculum***
- ***Bacteremia***
- ***Drug kinetics***
- ***Resistance***



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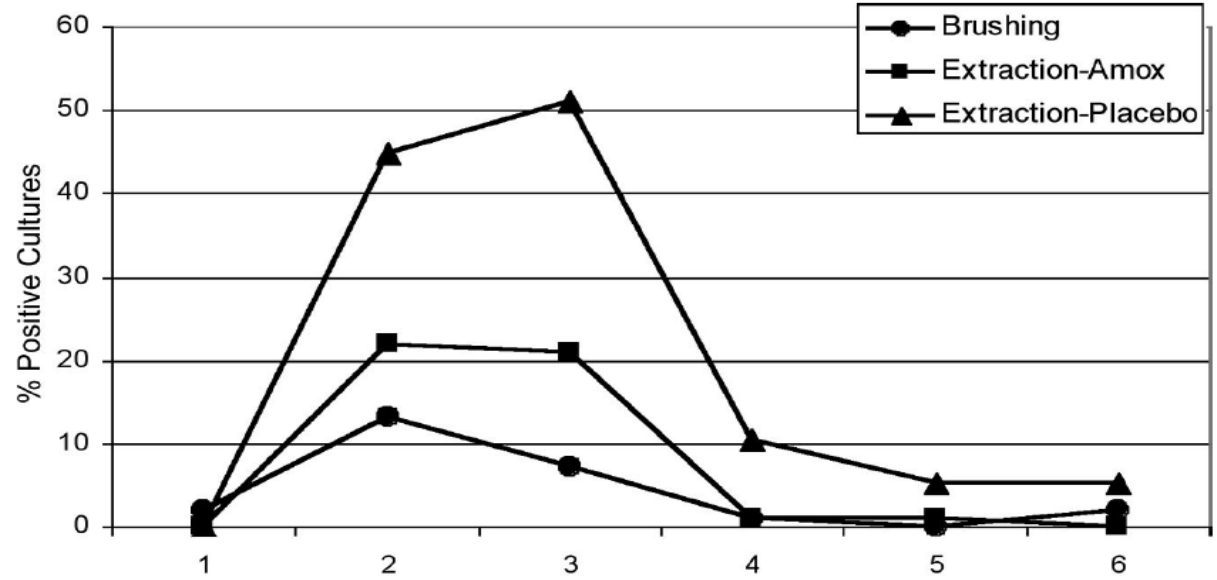
Bacteremia Associated With Toothbrushing and Dental Extraction

- 600 patients screened, 290 randomized
  - 98 toothbrushing
  - 96 extraction+amox
  - 96 extraction+Pcb
- 98 bacteremia
  - 32 IE-causing bacteria
  - Similar magnitudes (4 $\log_{10}$ CFU/ml) in all groups



Is antibiotic prophylaxis for dental extraction relevant?

Lockhart et al., Circulation. 2008;117:3118-3125

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Controlled clinical trial: an "urgent" need

- 1976: Lancet editorial
  - Prophylaxis of bacterial endocarditis: faith, hope, and charitable interpretations
- 1992: Lancet editorial
  - Most experts groups have shied away from suggesting prospective controlled studies of the efficacy of chemoprophylaxis on the argument that it would require an impractically large population. Surely it is time for this negative view to be reassessed. The EC, with its 330 million inhabitants might take the matter in hands. The doctrine of faith, hope, and charity may be a philosophy for life: it is no basis for perpetuating costly and possibly ineffective medical practices
- 2015: Lancet editorial (X. Duval, B. Hoen, Lancet 2015;385:1164)
  - Prophylaxis for infective endocarditis: let's end the debate

RCTs Of Antibiotic Prophylaxis (AP) to Prevent Infective Endocarditis (IE)

- Main reasons why no RCTs have been performed to date
  - Size, complexity and cost of a study
  - Ethical concerns – randomising patients to placebo or no AP

Attempts at performing an RCT

- 2006 NIH R21 – Clinical Trial Planning Grant – P. Lockhart *et al*
- 2011 NIHR HTA application – The APPROVED Clinical Trial – M.Thornhill, B. Prendergast, J. Nicholl *et al*
- 2012 NIH – The APPROVED Clinical Trial – M.Thornhill, B. Prendergast, J. Nicholl *et al*

The APPROVED clinical trial

***A**ntibiotic **P**rophylaxis **P**revention of **PRO**sthetic **V**alve **E**ndocarditis in **D**entistry*

Incident Patient Identification
12,000 new prosthetic valve patients pa >18 yrs old.
Valve replaced >1 year earlier

Prevalent Patient Identification
100,000 prosthetic valve patients >18 yrs old from UK National Cardiac Surgical Database.
Valve replaced >1 year earlier

4,880 patients pa

Recruitment
Through original surgical centre. Informed and consented by post. Edentulous patients excluded (20%). It is assumed that 50% of prevalent and 50% of incident cases will be recruited
Allergy history confirmed.

40,000 patients

Randomisation
Patient provided with AP or PP supplies and study pack

Antibiotic Prophylaxis (AP) Group
•Single 2g oral dose amoxicillin
Or if allergic to penicillin
•Single 600mg oral dose clindamycin

Placebo Prophylaxis (PP) Group

The APPROVED clinical trial

- Assessment: a good study design with high chance of delivering a clear outcome
- Estimate: 2 years - set up/approvals, publicise etc. 5 years data collection, 1 year analysis (Total 8 years)
- NIH priced study at US$60m (Euro 53m, £38m) i.e. x3
- About to consider funding when 2012 'Fiscal Cliff' financial crisis hit USA
- NIH required to stop all new funding
- 2013 – NIH Funding freeze lifted
- Politically US$60m now considered too high a cost for any RCT – particularly when entirely outside USA

How to assess the efficacy of antibiotic pophylaxis of IE in humans? Searching for innovative designs: could a randomized registry-based trial solve the problem?

Contributors

François Alla, Xavier Duval, Nelly Agrinier, and Bruno Hoen

What about a randomized registry-based trial?

- It has already been done and (well) published
  - Screening and Prostate-Cancer Mortality in a Randomized European Study (N Engl J Med 2009;360:1320-8)
  - Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction (N Engl J Med 2013;369:1587-97)
- What is a registry-based randomized trial?
  - A registry-based trial is a RCT conducted within or with the help of a registry (the registry is used to identify patients and/or to replace the CRF and/or to carry out the follow-up)
  - Numerous advantages
    - a rigorous randomized experiment that can test a causal link between a treatment and an outcome
    - because inexpensive, investigators can enroll large numbers of patients
    - realworld population created from existing consecutively registry-enrolled patients, which makes it possible to assess effectiveness in addition to efficacy

How could a registry-based randomized trial be implemented for AP of IE?

- Population (registry-based)
  - Registries make it possible to identify (all) people with high-risk conditions (prosthetic valve, other…)
- Randomization (not registry-based but cluster-based)
  - Geographic area
  - Dentist's patients
- Follow-up and Endpoint (registry-based)
  - National hospital discharge diagnosis database
  - Advantage
    - virtually all IE cases are diagnosed and treated in hospitals
  - Drawbacks
    - Diagnosis of IE would not be expert-validated
    - Causative microorganism may not be reported

How could a registry-based randomized trial be implemented for AP of IE? Situation in France (1)

- The French National Health Insurance information system (SNIIRAM), anonymously collects all individual and health care claims reimbursed by the French National Health Insurance (covering the whole French population). It is linked/merged with the French Hospital Discharge database (PMSI), which contains discharge diagnoses (ICD-10 codes) and medical procedures for all patients admitted to hospital in France
- From this database it would be possible to
  - set up a cohort of patients with prosthetic valves
  - observe and define a target dental intervention during follow-up
  - whether or not antibiotic prophylaxis would be used for this target intervention (whatever the randomization arm),
  - Identify the occurrence of an IE and compare incidence of IE between groups

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Dental and cardiac risk factors for IE: a population-based, case-control study.

- Methods
  - 273 cases of community-acquired IE
  - 273 controls matched by age, sex, and neighborhood
- Results
  - Pre-existing cardiac disease:
    - OR = 16.7 (IC95 : 7.4 – 37.4)
  - Dental procedures within past 3 months:
    - OR = 0.8 (IC95 : 0.4 – 1.5)
  - Very few patients received antibiotic prophylaxis, in either group
- Interpretations
  - Few cases of IE could be prevented with prophylaxis even if 100% effective
  - Current policies for prophylaxis should be reconsidered.

B. Strom et al. Ann Intern Med 1998;129:761.

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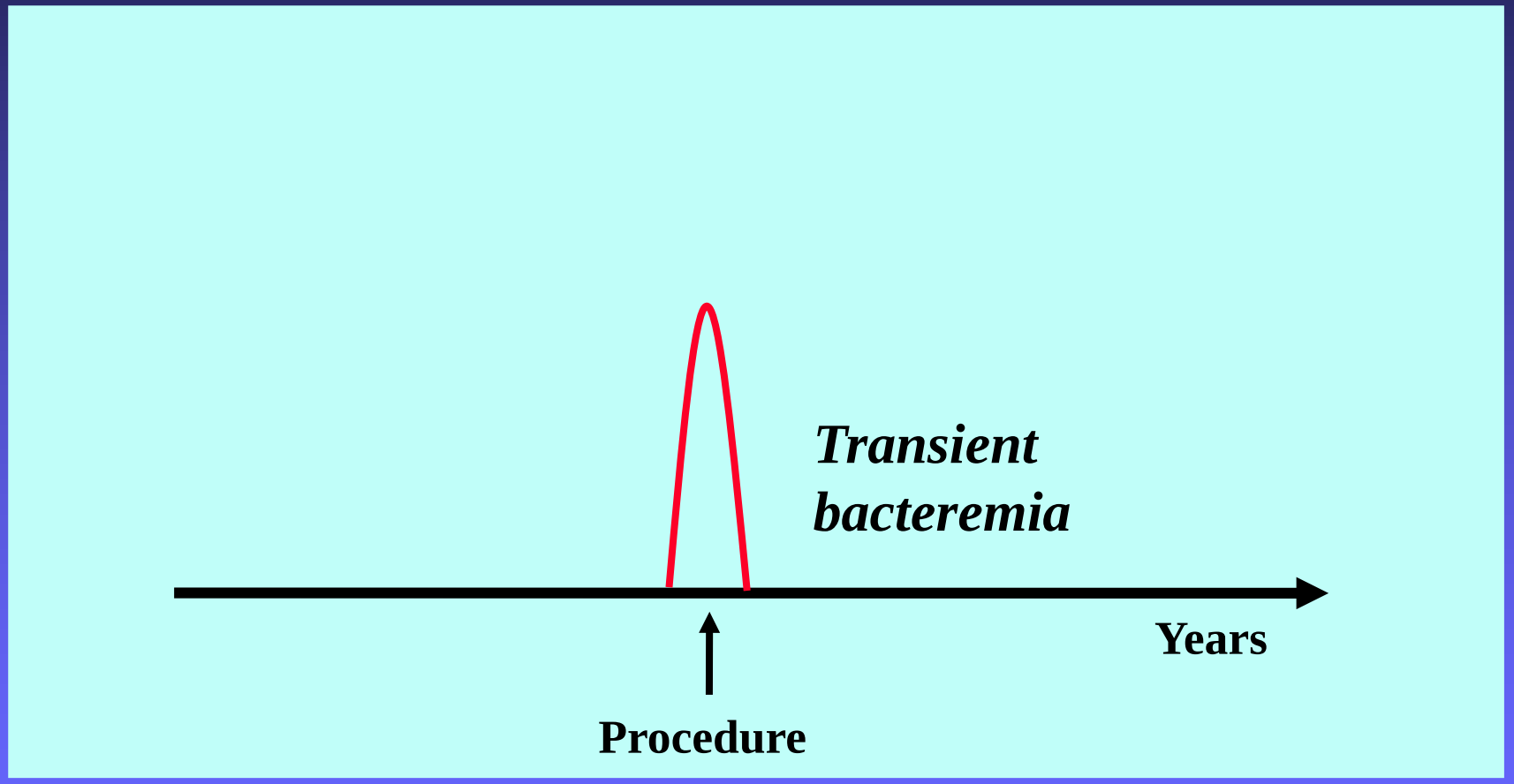
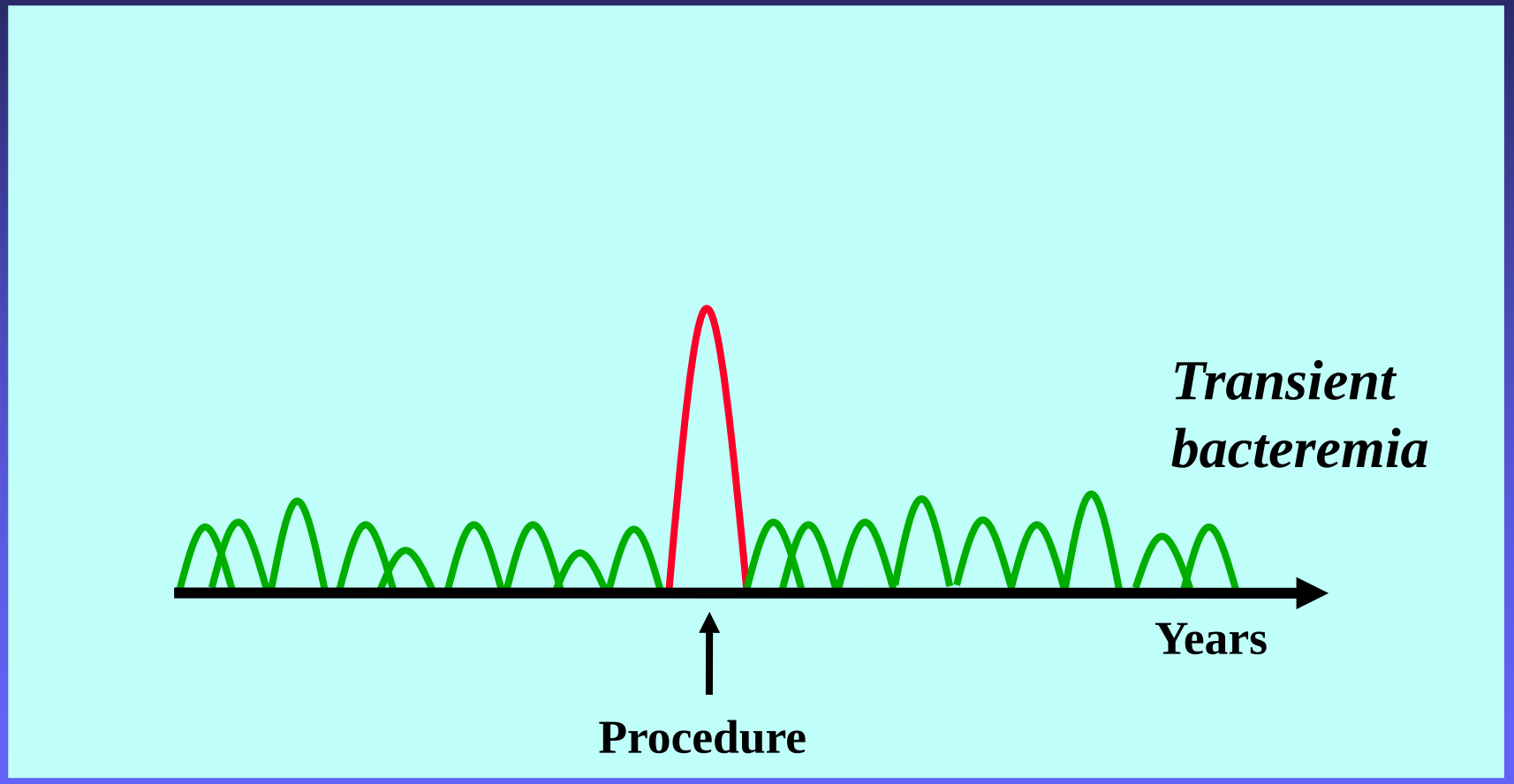
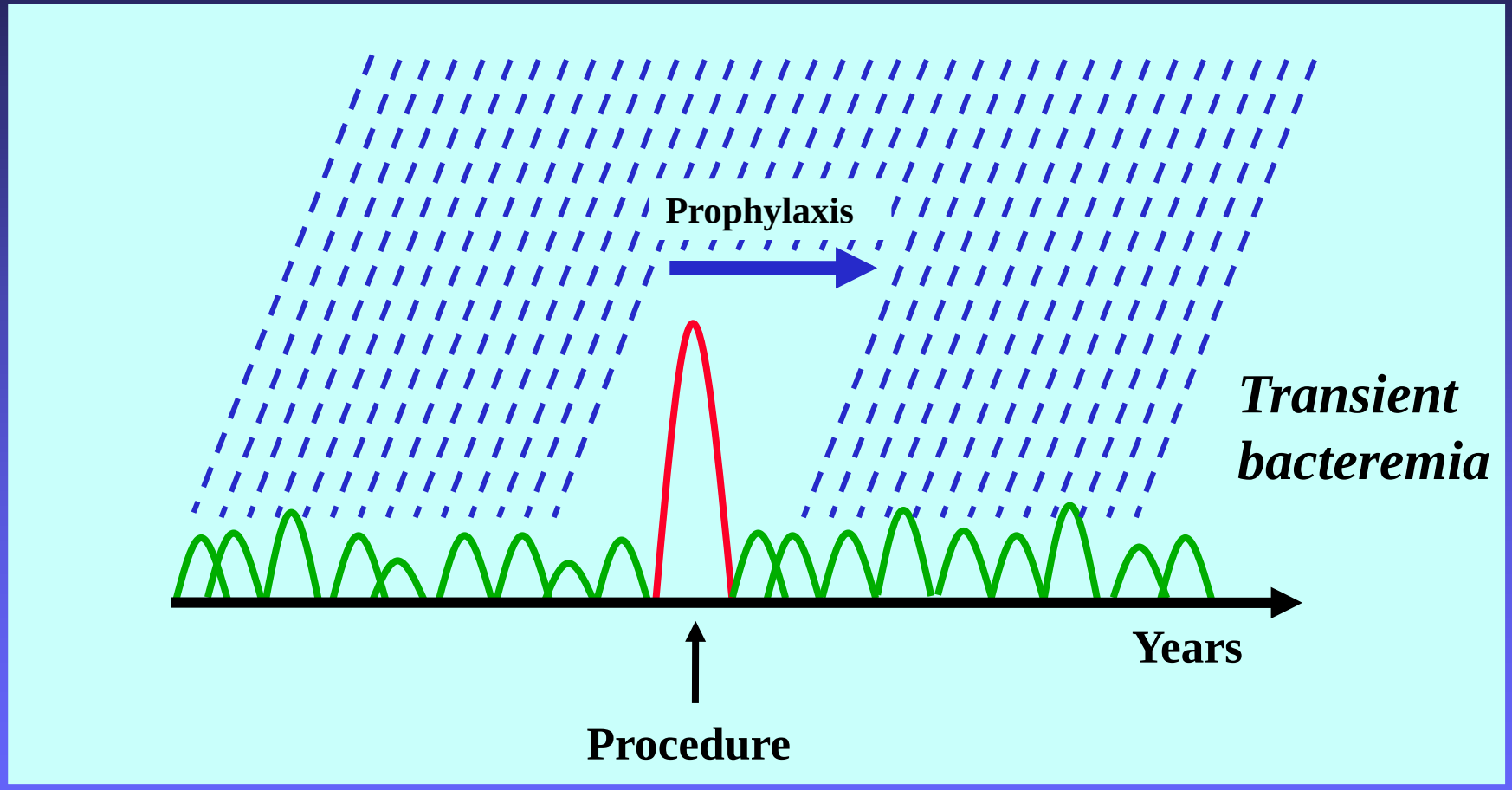
Procedure-induced Bacteremia



Overall Transient Bacteremia



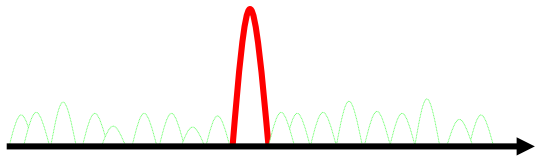
Limited Effect of Antibiotic Prophylaxis



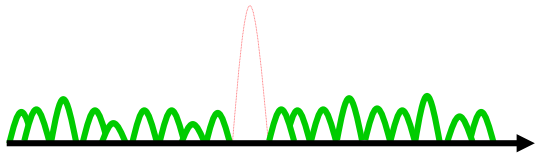
Cumulative bacteremia and risk of IE in a rat model

S. gordonii

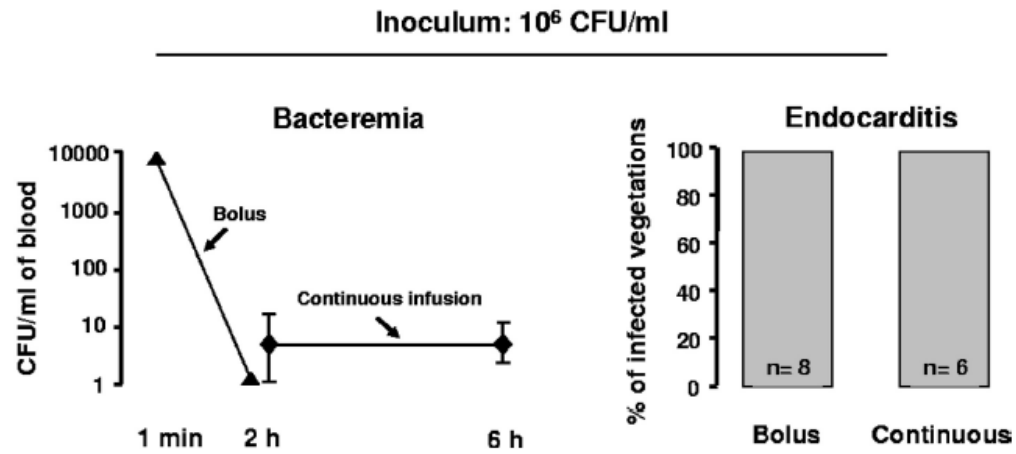
SAME INOCULUM



Bolus
1 ml / 1 min



Continuous infusion
0,0017 ml/min over 10 h



Veloso,TR, Infect Immun 2011; 79:2006

BMJ 2017;358:j3776

Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves: nationwide population based cohort and a case crossover study

Sarah Tubiana,[1,2] Pierre-Olivier Blotière,[2] Bruno Hoen,[3] Philippe Lesclous,[4] Sarah Millot,[5] Jérémie Rudant,[2] Alain Weill,[2] Joel Coste,[2] François Alla,[2] Xavier Duval[1]

- Cohort: 138 876 adults with PHV (285 034 person years)
  - 69 303 (49.9%) underwent at least one dental procedure
  - 396 615 dental procedures were performed
    - 103 463 (26.0%) were invasive and presented an indication for AP
    - which was performed in 52 280 (50.1%)
  - With a median follow-up of 1.7 years, 267 people developed IE due to oral streptococci (93.7 per 100 000 person years)
  - Compared with non-exposure periods, no statistically significant increased rate of oral streptococcal IE was observed
    - during the three months after an invasive dental procedure
    - after an invasive dental procedure without antibiotic prophylaxis

BMJ 2017;358:j3776

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- In the case crossover analysis, exposure to invasive dental procedures was more frequent during case periods than during matched control periods
  - 5.1% v 3.2%
  - odds ratio 1.66, 95% CI 1.05 – 2.63; P=0.03

Antibiotic prophylaxis of IE: summary of evidence

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- Human experimental trials showed that penicillin prophylaxis reduces the incidence of bacteremia after dental extraction
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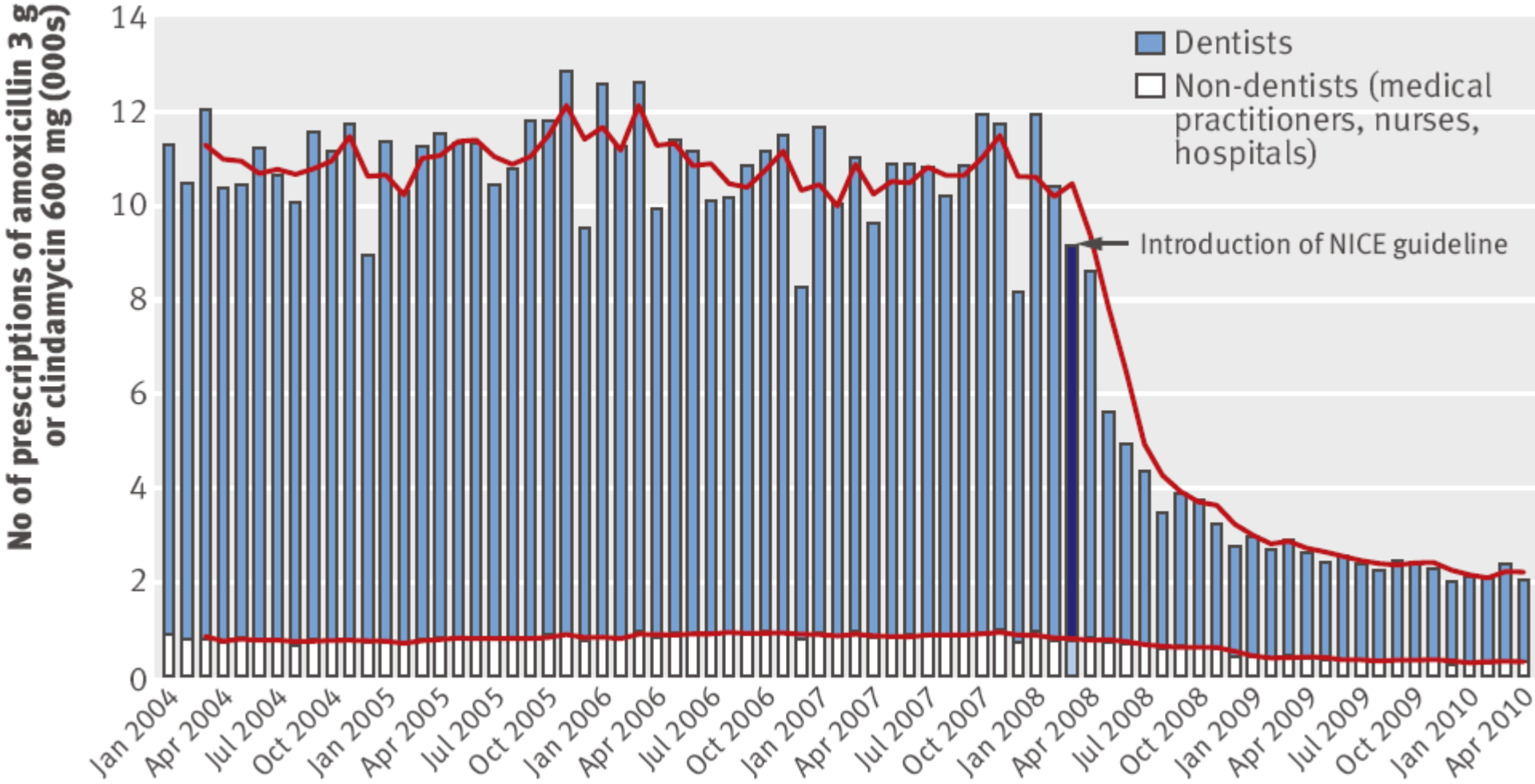
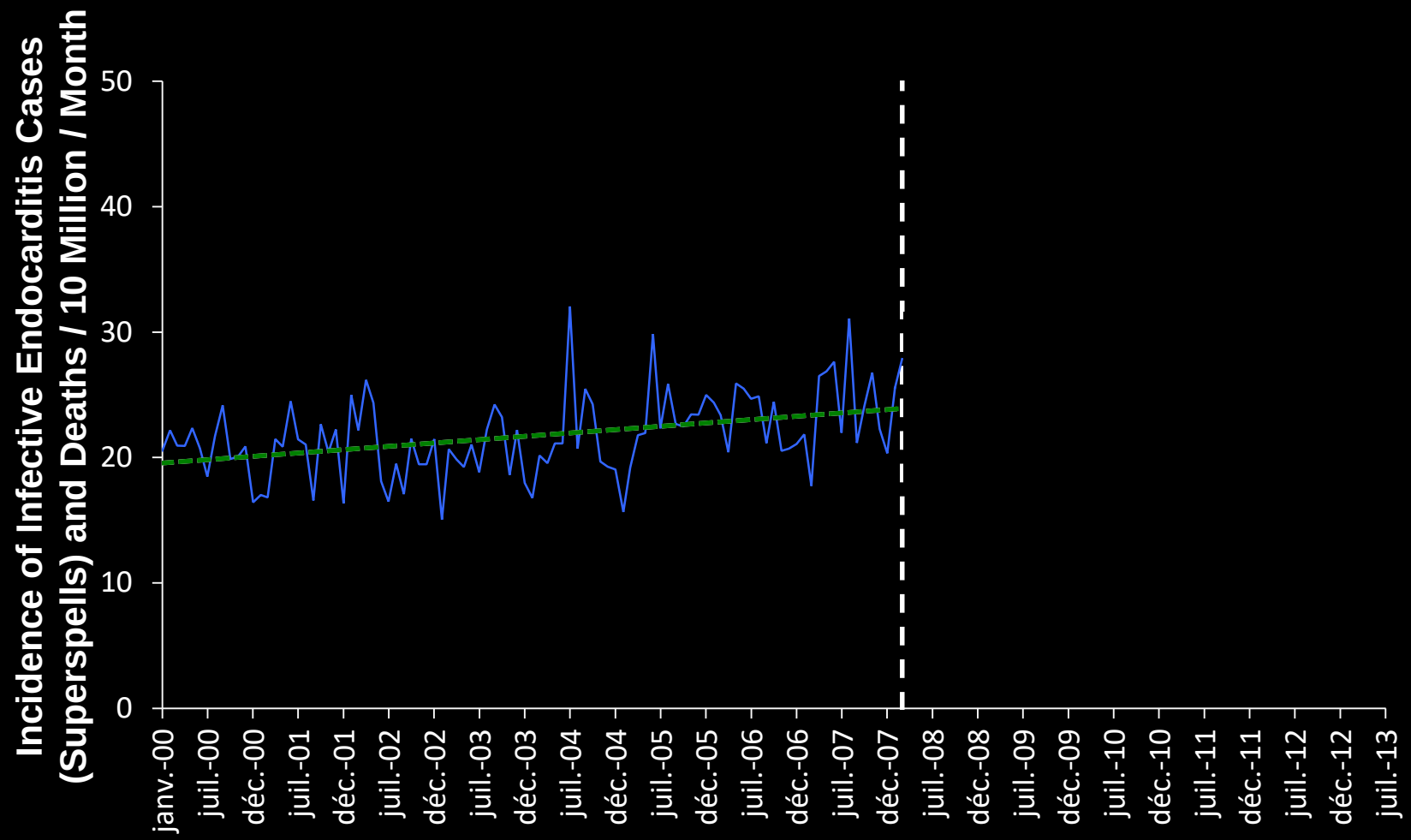
Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of IE



Thornhill MH, BMJ 2011;342:d2392 doi:10.1136/bmj.d2392

Incidence of IE



Dayer M, Lancet 2015;395:1219

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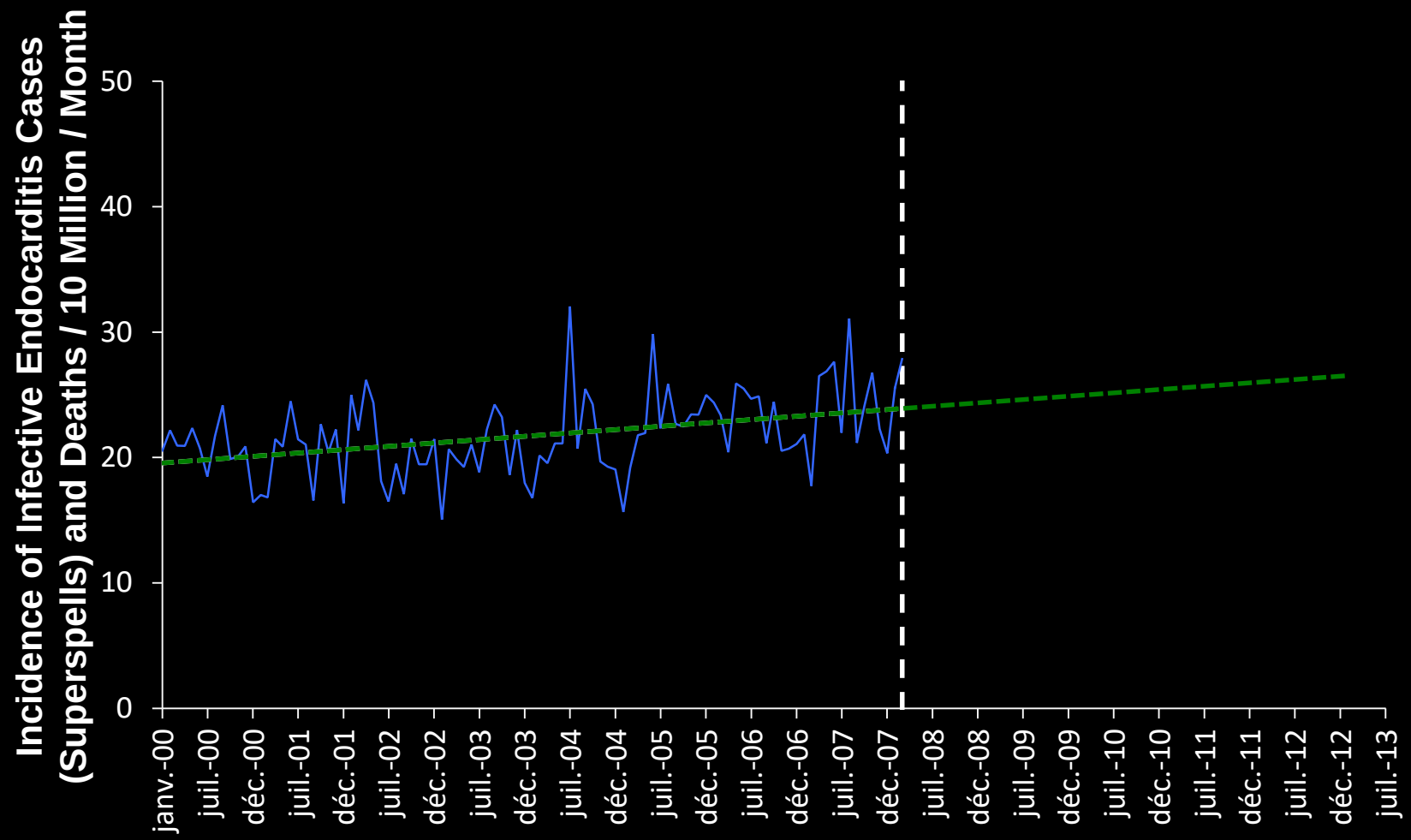

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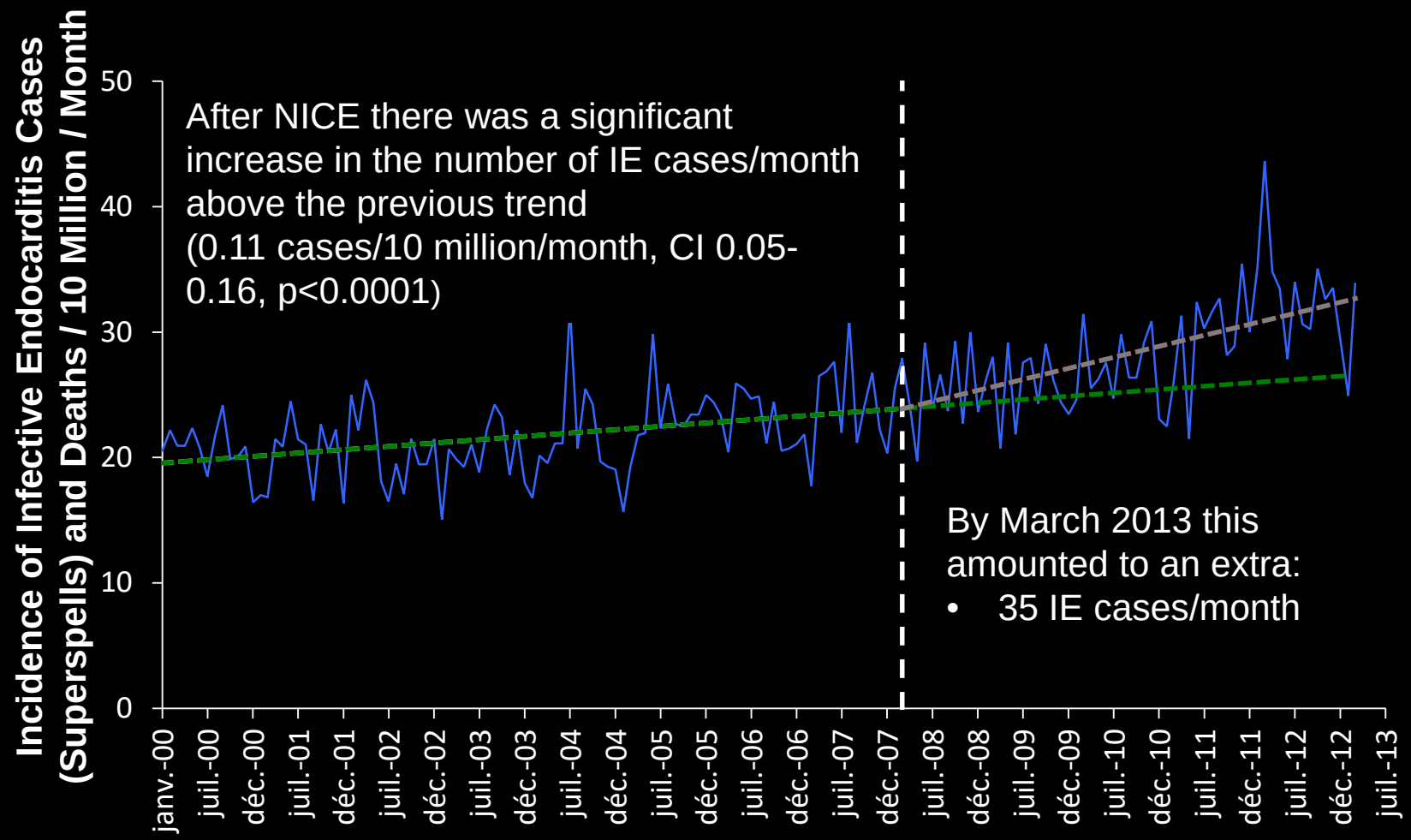

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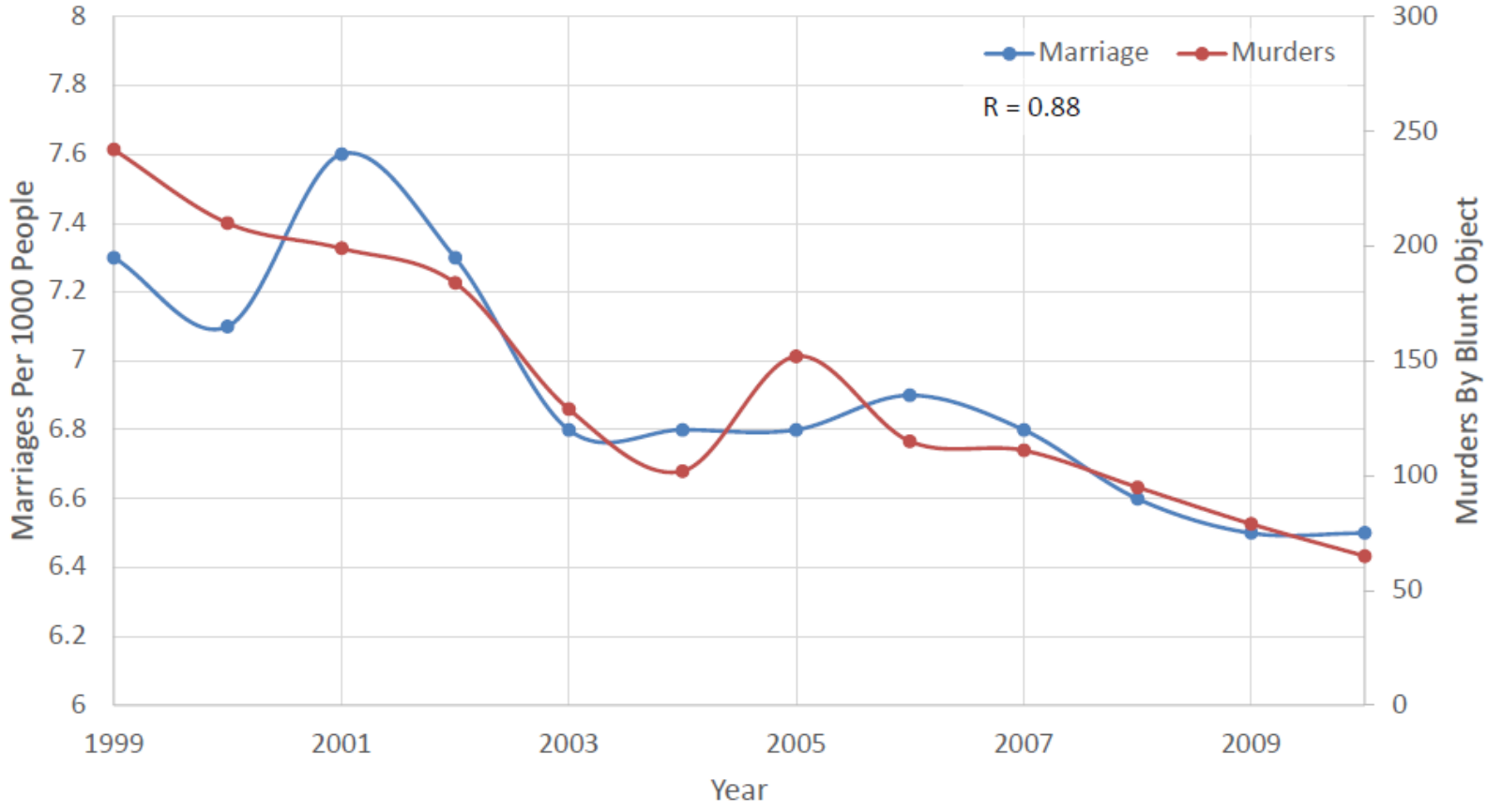
Time trend studies addressing the changing population incidence of infective endocarditis after guideline changed

Paper	Study location	Population/diagnoses analyzed	Incidence change?
Bikdeli, 2013[134]	USA	All diagnoses of IE from Medicare Inpatient Standard Analytic Files	No evidence of an increase in adjusted rates of hospitalization or mortality after 2007 guideline change
Dayer, 2015[5] Thornhill, 2011[35]	England, UK	All diagnoses of IE from NHS Hospital Episode Statistics	In the 2015 analysis there was an increase detected in the number of cases of IE above the projected historical trend (by 0.11 cases per 10 million people per month). Statistical analysis identified June 2008 as the change point (3 months after NICE guideline change).
De Simone, 2015[33] DeSimone, 2012[32]	Olmsted County, Minnesota, USA	Diagnoses of VGS IE from Rochester Epidemiology Project	No evidence of an increase in VGS IE
Duval, 2012[135]	France – Greater Paris, Lorraine, and Rhône-Alpes	All diagnoses of IE and subgroups by specific organisms	No evidence of an increase in VGS IE
Mackie, 2016[34]	Canada	Diagnoses of IE from Canadian Institute for Health Information Discharge Abstract Database	No significant change in the rate of increase in IE cases after publication of guideline change. Reducing incidence of VGS IE over time. Change point analysis did not identify guideline change as a significant inflection point.
Pant, 2015[2]	USA	Diagnosis of IE using Nationwide Inpatient Sample	Significant increase in the rate of rise in strep IE after 2007 (change in the slope before and after = 1.37 95% CI 0.69 – 2.05, p = 0.002). No change point analysis.

Marriage Rate in New York and Murders by Blunt Object



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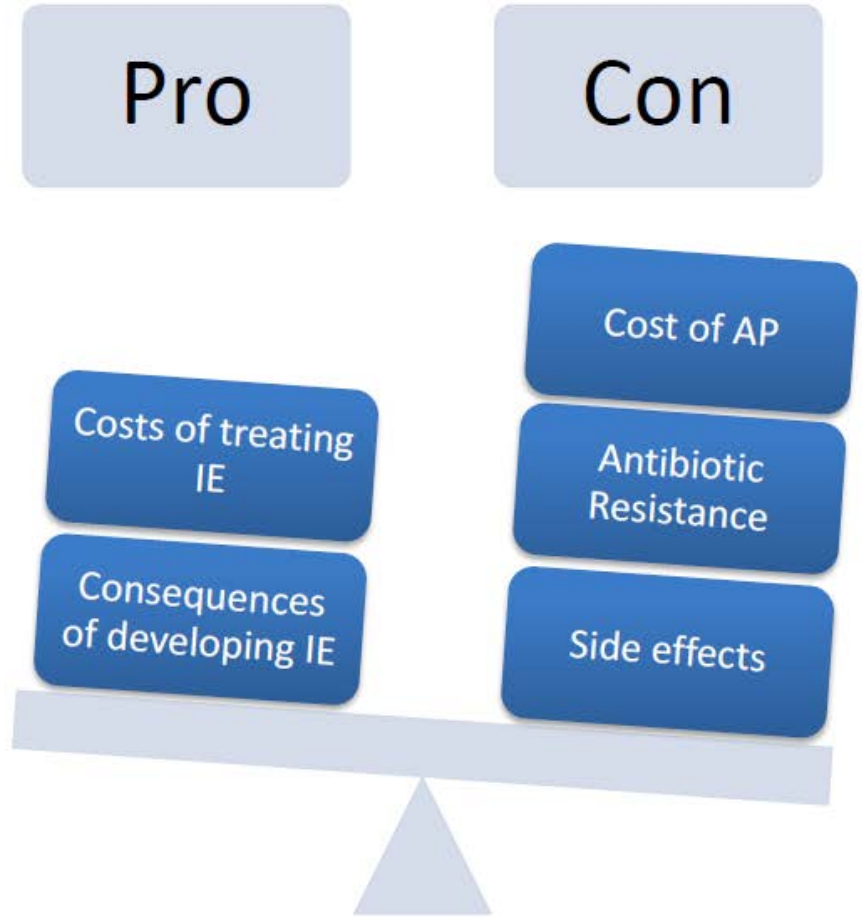
In the fog?

What to do?


Pro
Con
Cost of AP
Costs of treating IE
Antibiotic Resistance
Consequences of developing IE
Side effects

Let's be pragmatic: AP for whom?

Indication	ESC guidelines 2015	Class/Evidence
Patient population	1. Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair. 2. Patients with previous IE 3. Patients with CHD, including a. Any type of cyanotic CHD b. Any type of CHD repaired with a prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains	IIa C
Procedure	Dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa	IIa C

Let's be pragmatic: what AP regimen?

Recommended prophylaxis

Recommended prophylaxis for dental procedures at risk			
		Single dose 30-60 minutes before procedure	
Situation	**Antibiotic**	**Adults**	**Children**
No allergy to Penicillin or Ampicillin	Amoxicillin or Ampicillin (1)	2 g p.o. or i.v.	50 mg/kg p.o. or i.v.
Allergy to Penicillin or Ampicillin	Clindamycin	600 mg p.o. or i.v.	20 mg/kg p.o. or i.v.

IE prophylaxis card

SPILF
SFC / FFC
SFCTCV ADF

PRÉVENTION DE L'ENDOCARDITE INFECTIEUSE

Actualisation 2011 des recommandations

Nom, prénom : .....

Cardiopathies à haut risque d'endocardite infectieuse :

❑ Prothèse valvulaire cardiaque ou anneau valvulaire
❑ Antécédent d'endocardite infectieuse
❑ Cardiopathie congénitale cyanogène

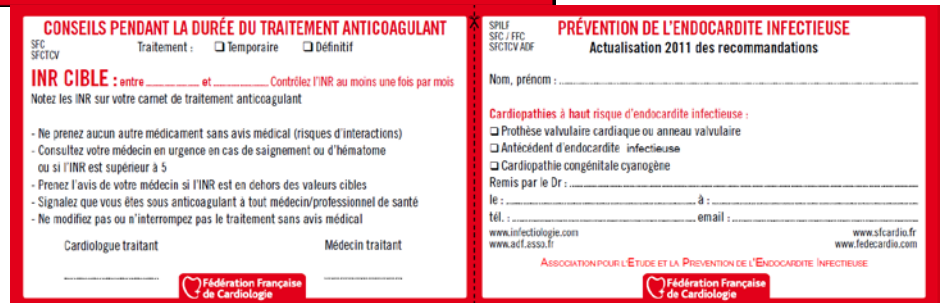
Remis par le Dr : .....
le : ..... à : .....
tél. : ..... email : .....

www.infectiologie.com
www.adf.asso.fr

www.sfcardio.fr
www.fedecardio.com

ASSOCIATION POUR L'ETUDE ET LA PREVENTION DE L'ENDOCARDITE INFECTIEUSE

Fédération Française de Cardiologie




Thank you for your attention