Prévention de l'endocardite infectieuse : entre trop et trop peu ?

Bruno Hoen
Université de Lorraine - CHU de Nancy
17 septembre 2018

Expert guidelines & consensus conferences

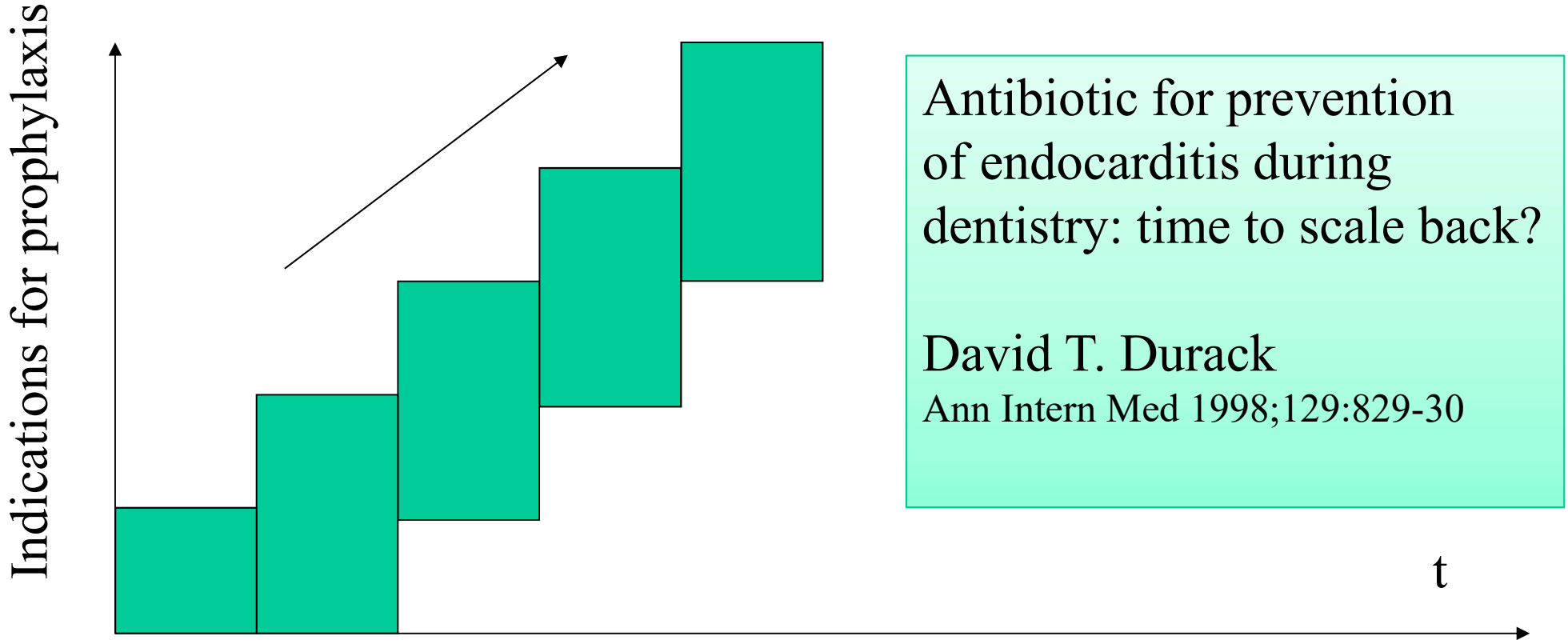
- USA (AHA):
  - 1954, 1965, 1977, 1984, 1990, 1997, 2007, 2014
- GB :
  - 1982, 1986, 1990, 1992, 2006 (BSAC)
  - 2008 (NICE)
- Switzerland
  - 1984, 2000
- France (SPILF/AEPEI)
  - 1992, 2002
- Europe (ESC/ESCMID)
  - 2004, 2009, 2015

- "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

Existing guidelines for IE prophylaxis in 2002

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



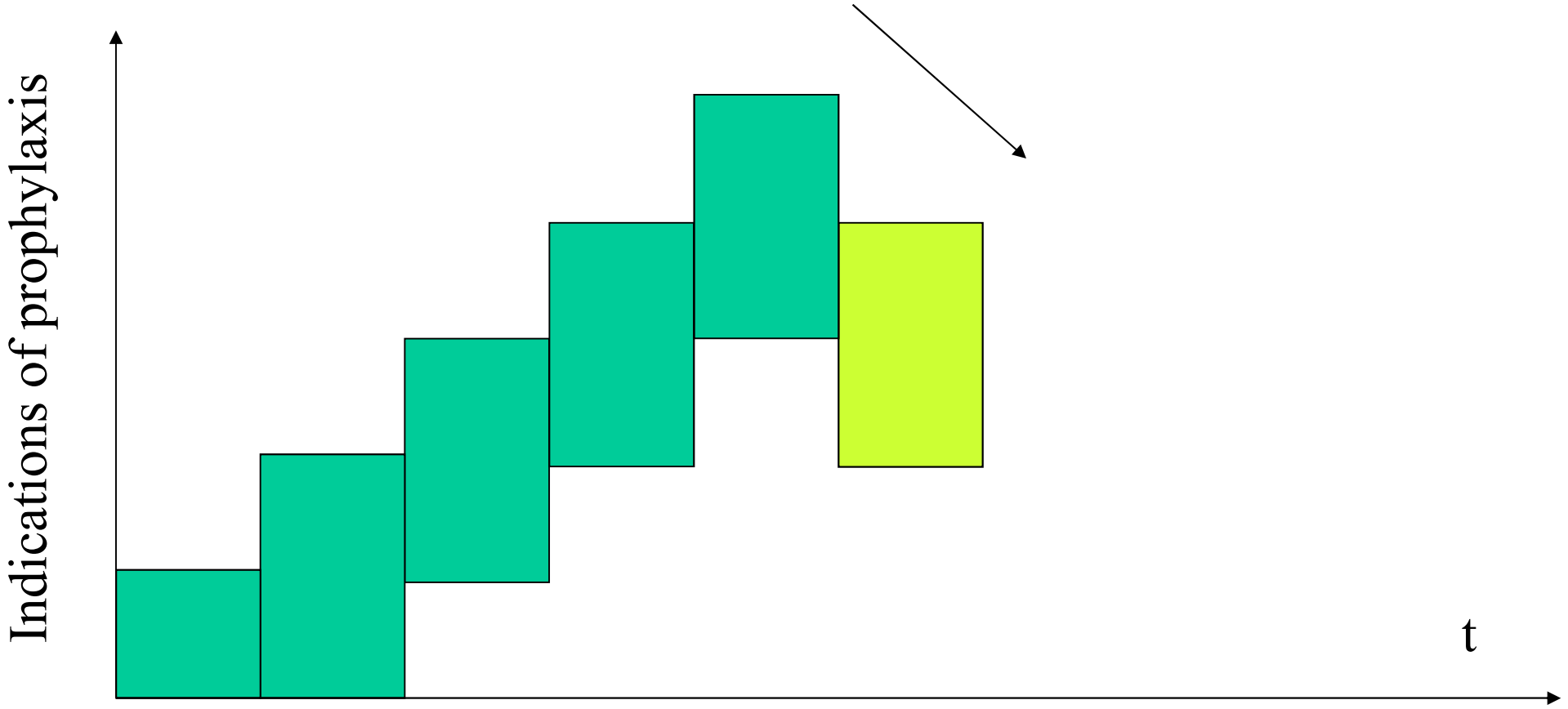
Antibiotic for prevention of endocarditis during dentistry: time to scale back?

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

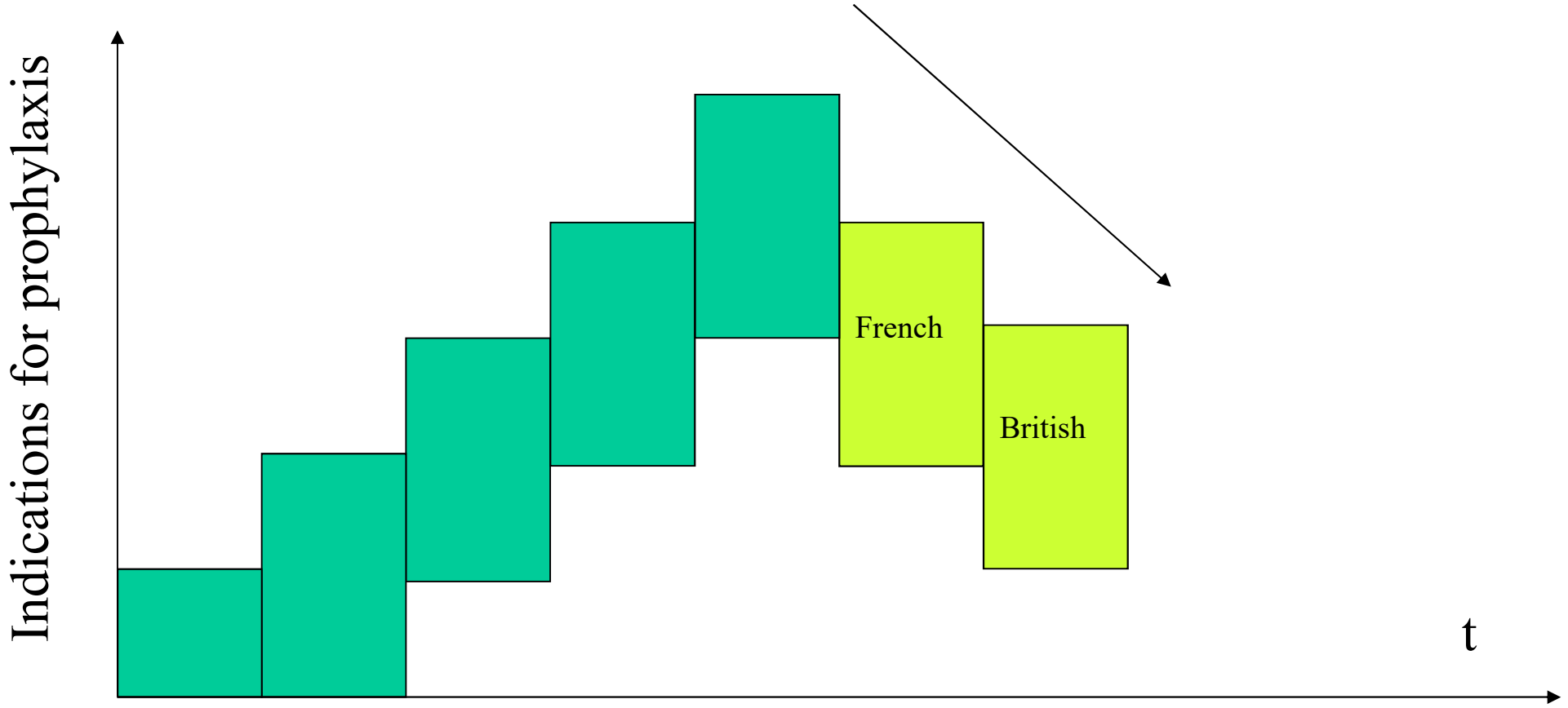
Prophylaxis of infective endocarditis: French recommendations 2002

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

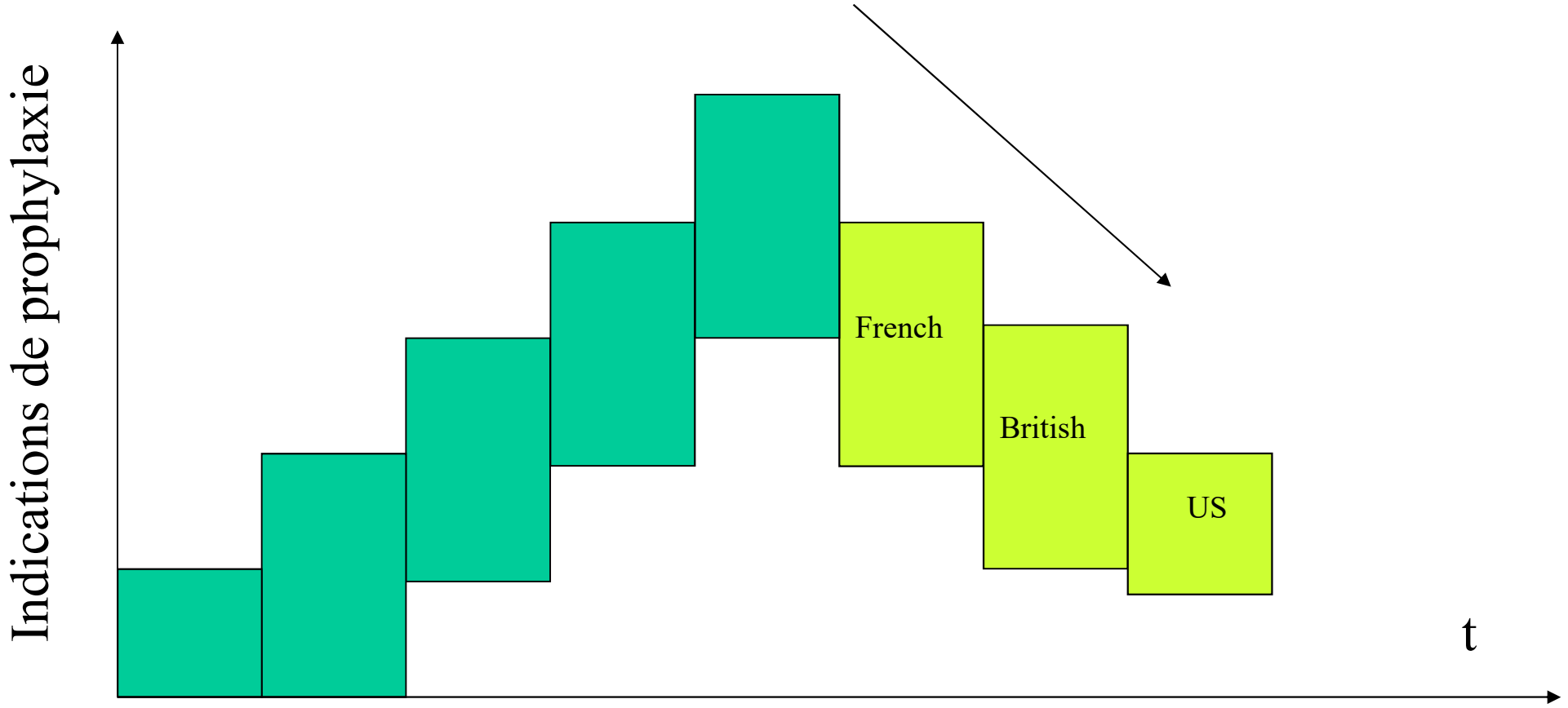
All dental procedures involving dento-gingival manipulation

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

Primary Reasons for Revision of the IE Prophylaxis Guidelines

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Wilson W, Circulation. 2007

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

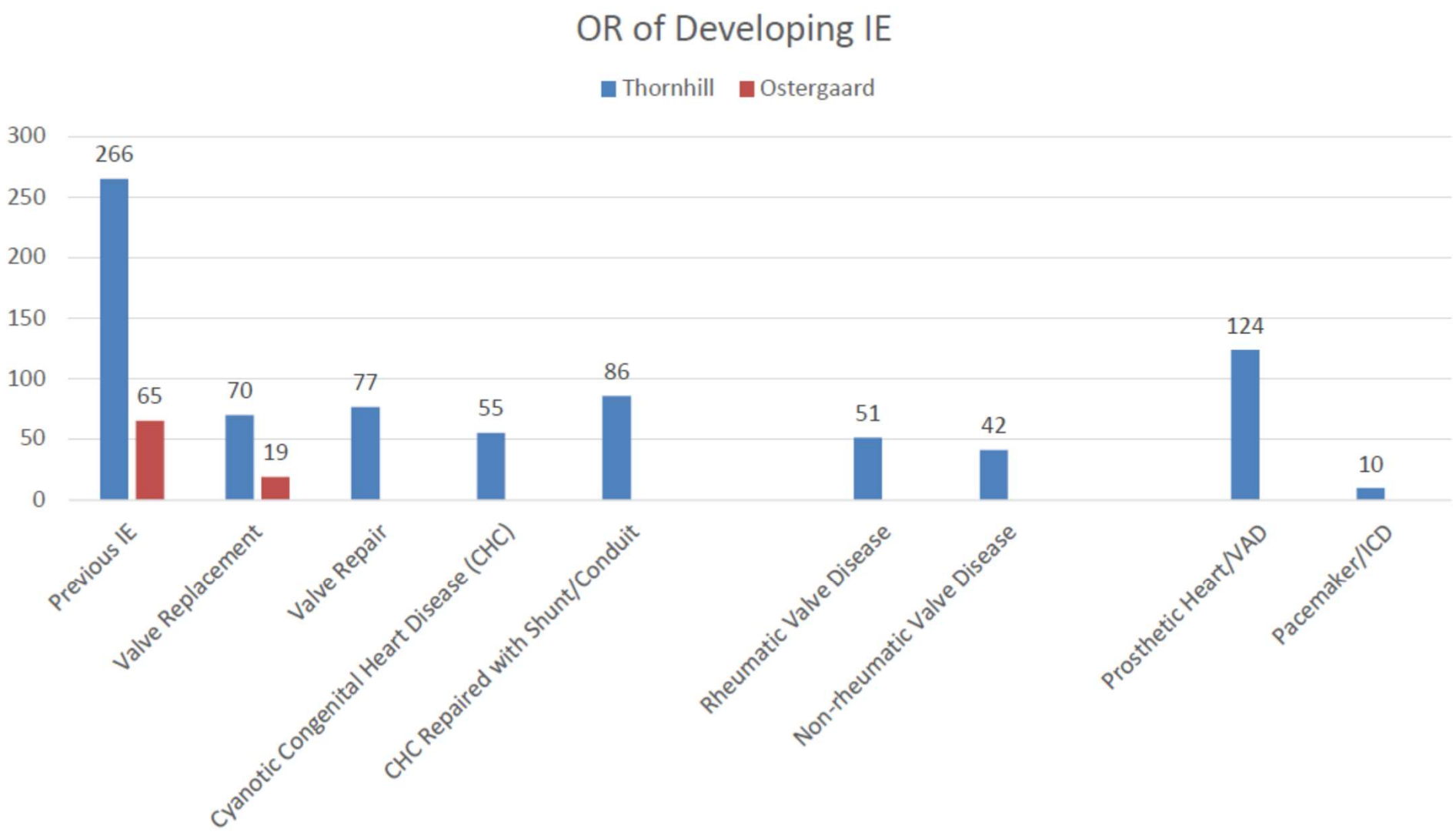
Prevention of IE: Guidelines from the AHA

- 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

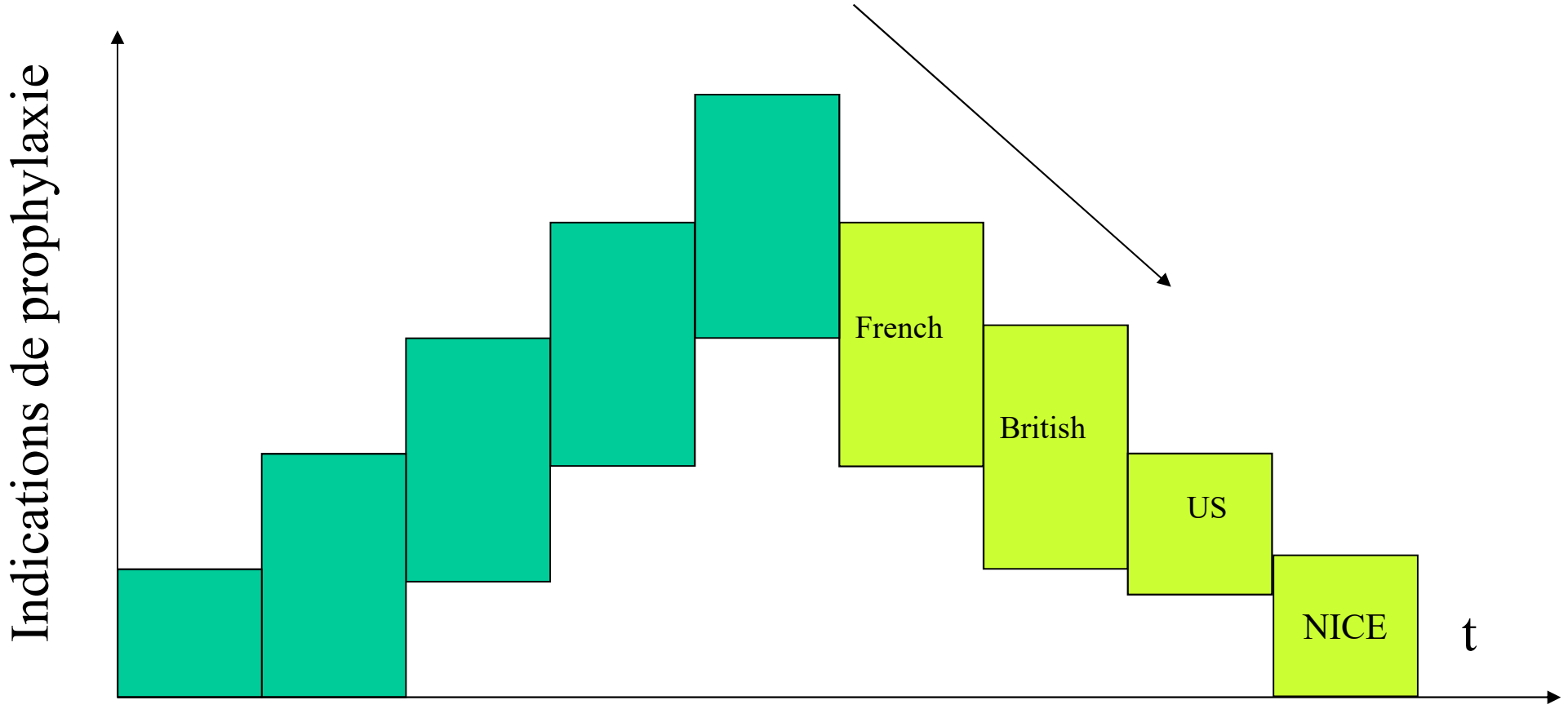
Thornhill et al. 2018, Ostergaard et al. 2018

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

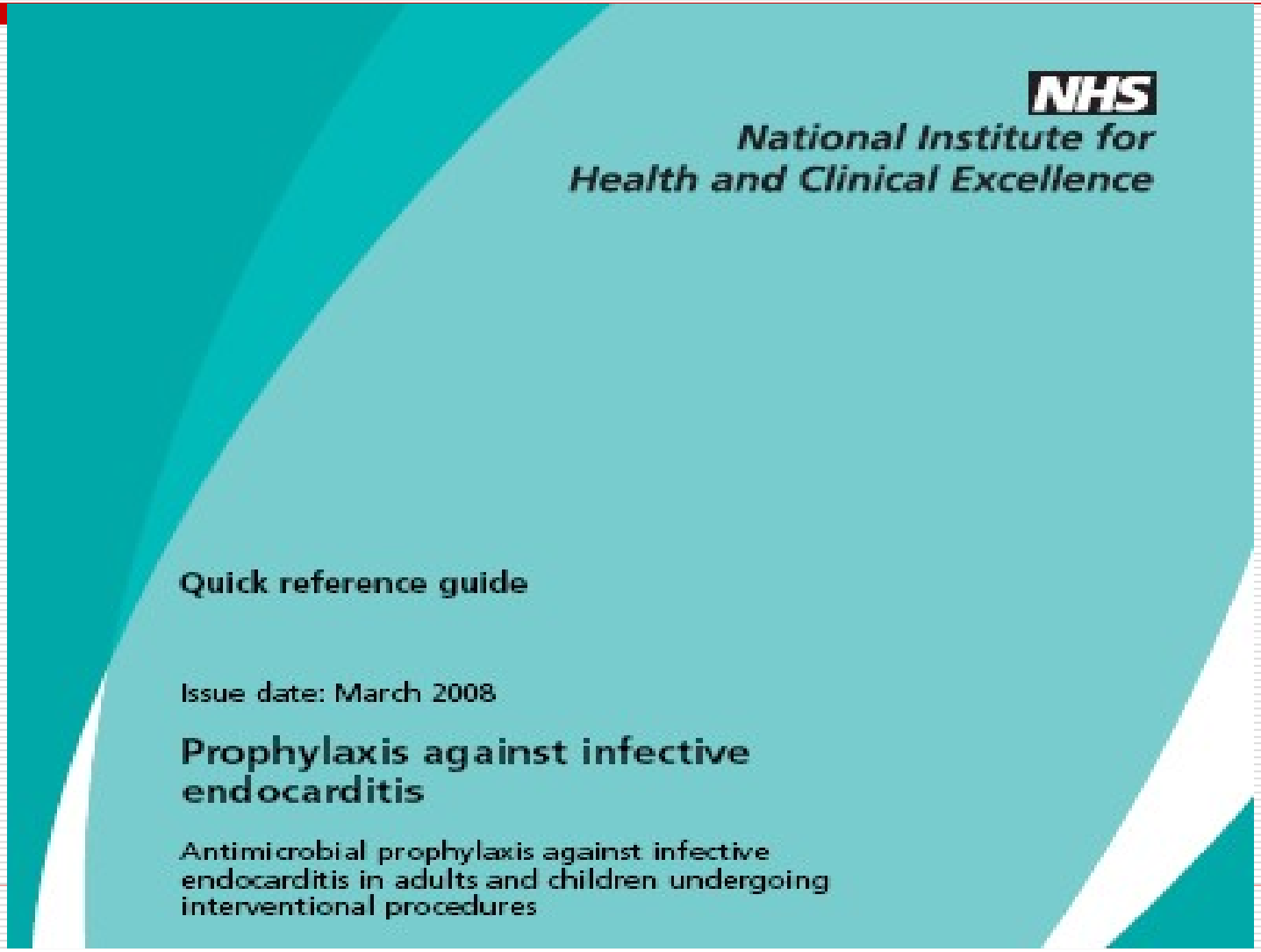


Mars 2008 : UK NICE clinical guideline

Exit l'antibioprophylaxie



AP against IE is NOT RECOMMENDED!



www.nice.org.uk/CG064

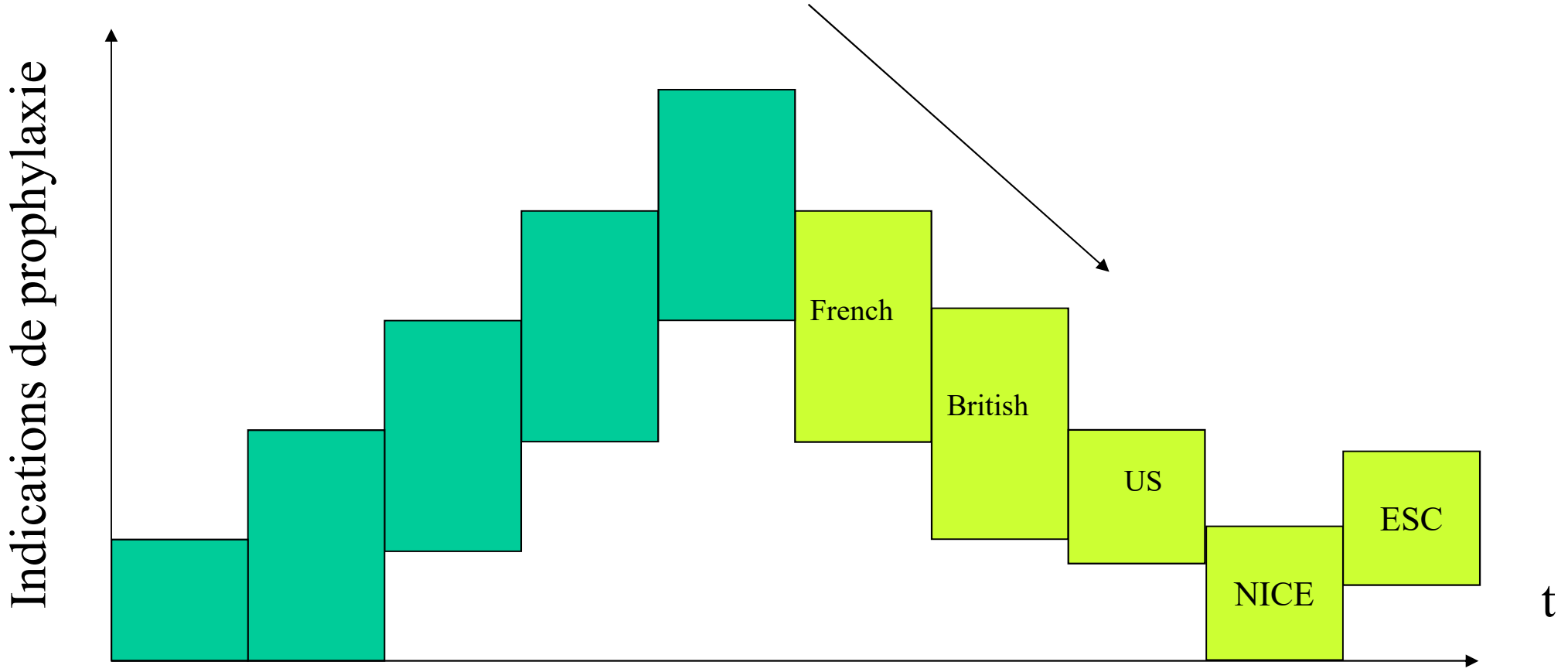
National Institute for Health and Clinical Excellence : prophylaxis against infective endocarditis

- 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
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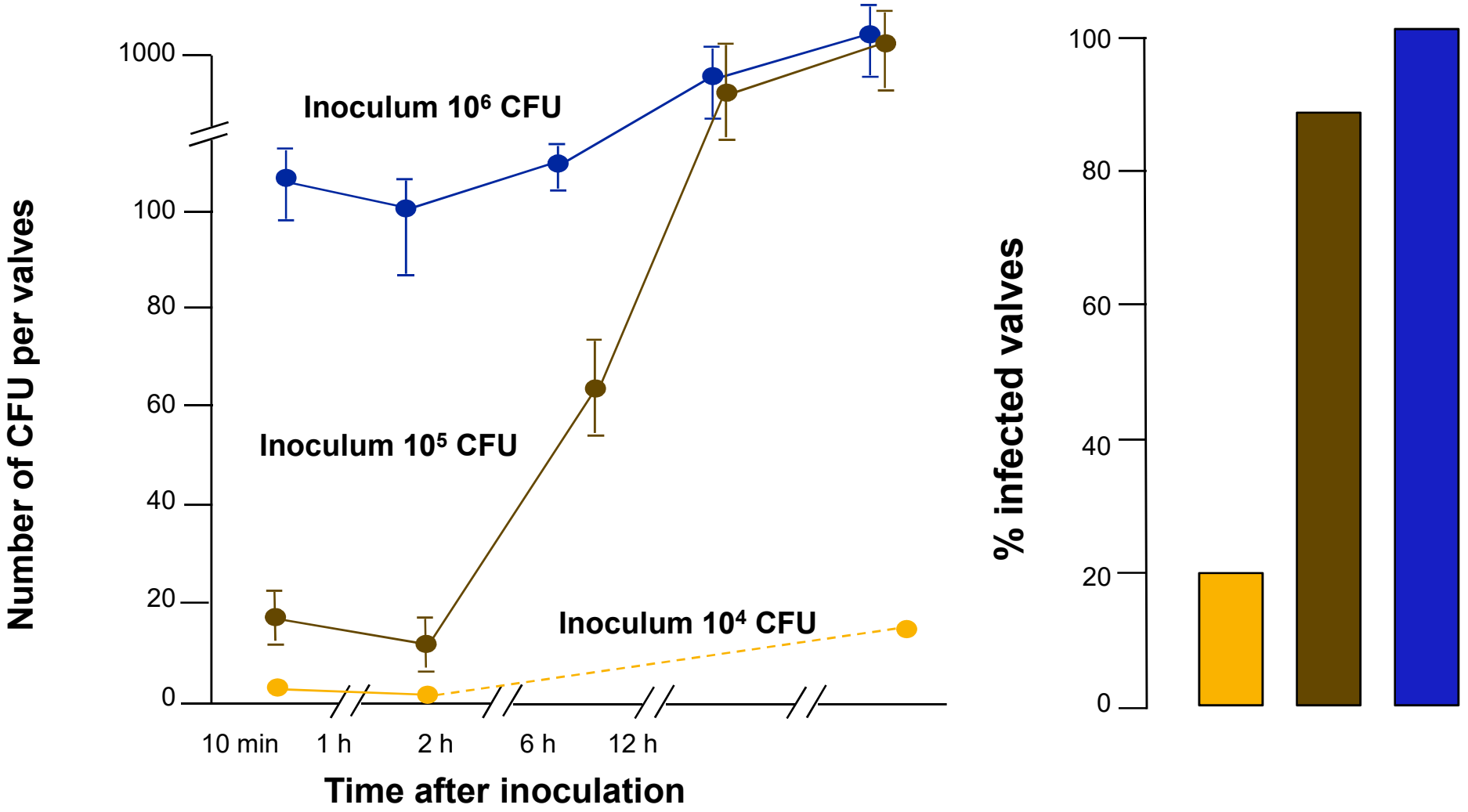
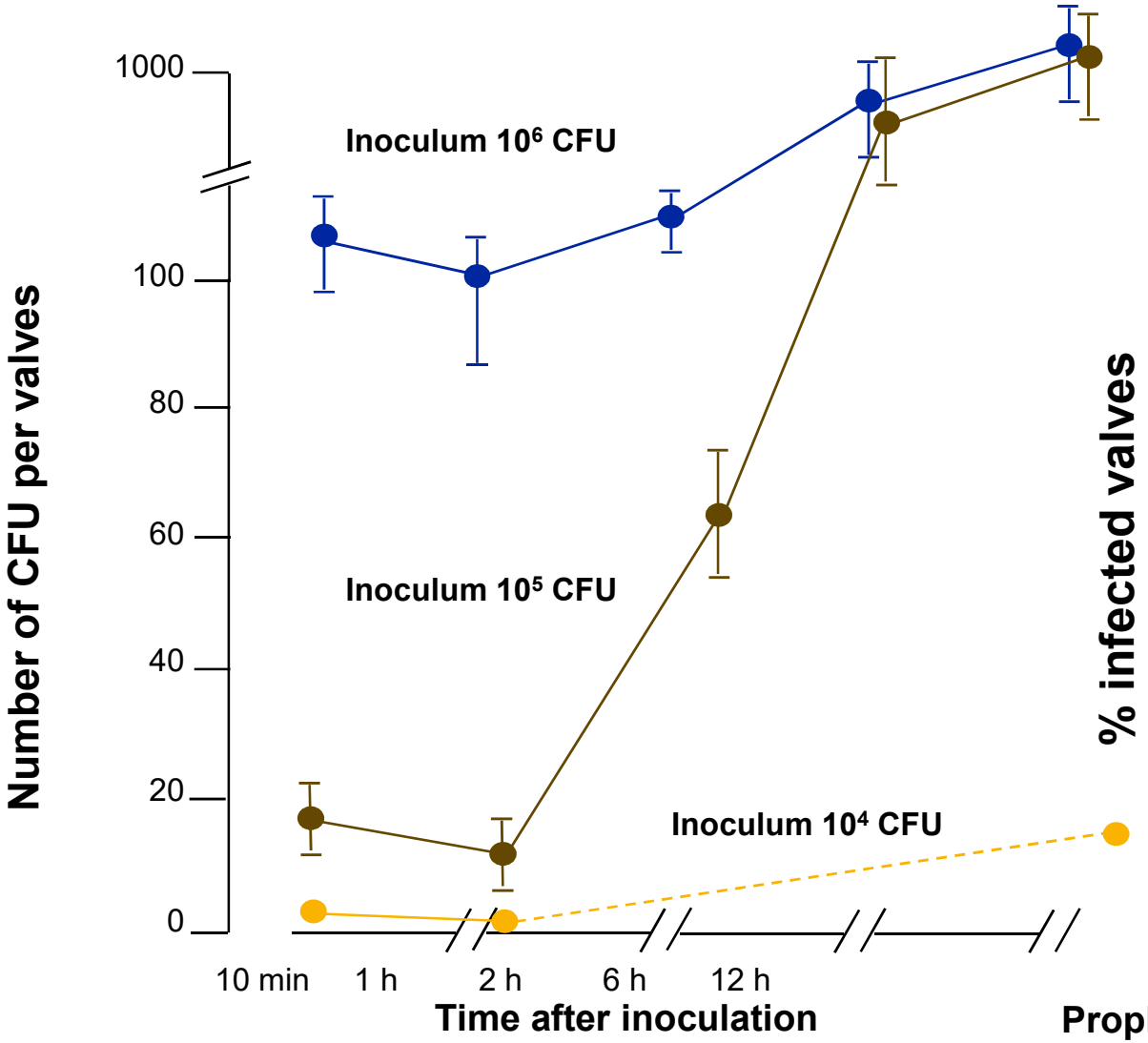
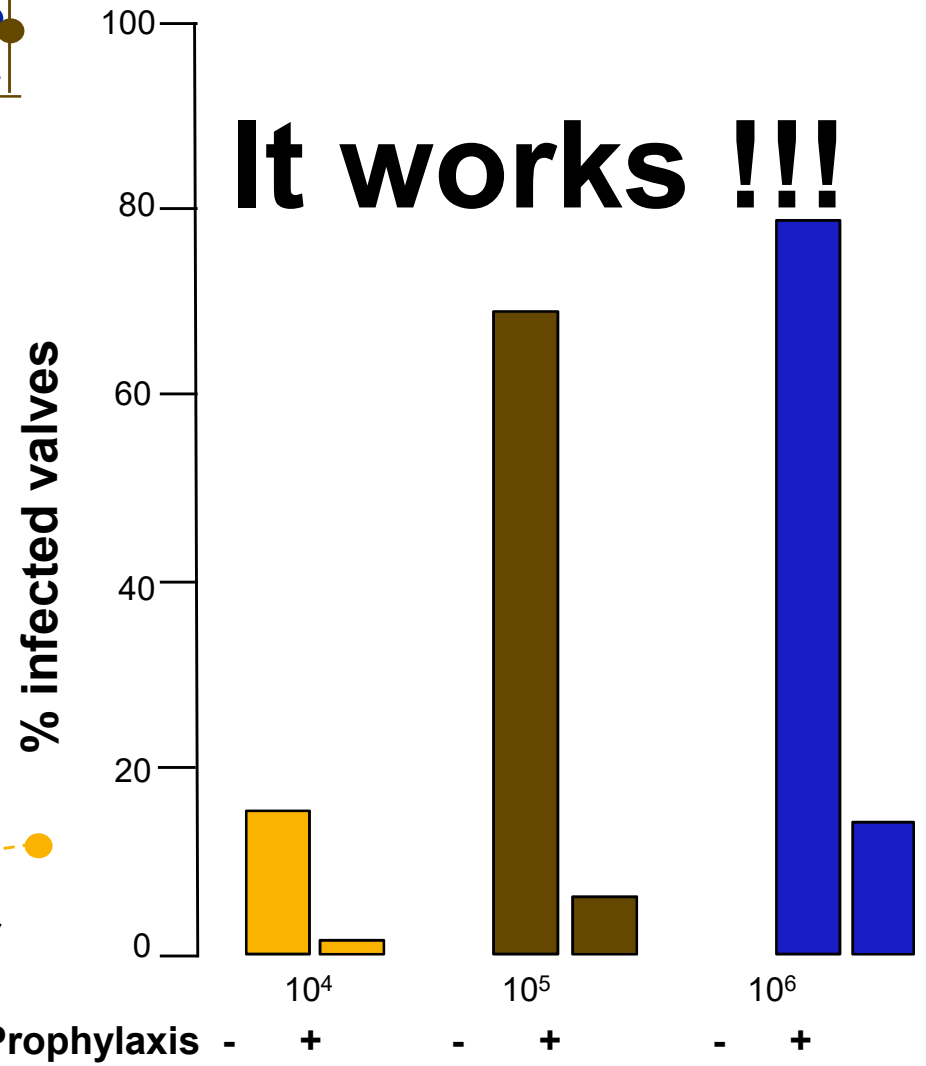
Effect of Bacterial Inoculum on Exp. IE Initiation



P Moreillon – UNI Lausanne

Single-dose Amoxicillin Prophylaxis in Streptococcal IE

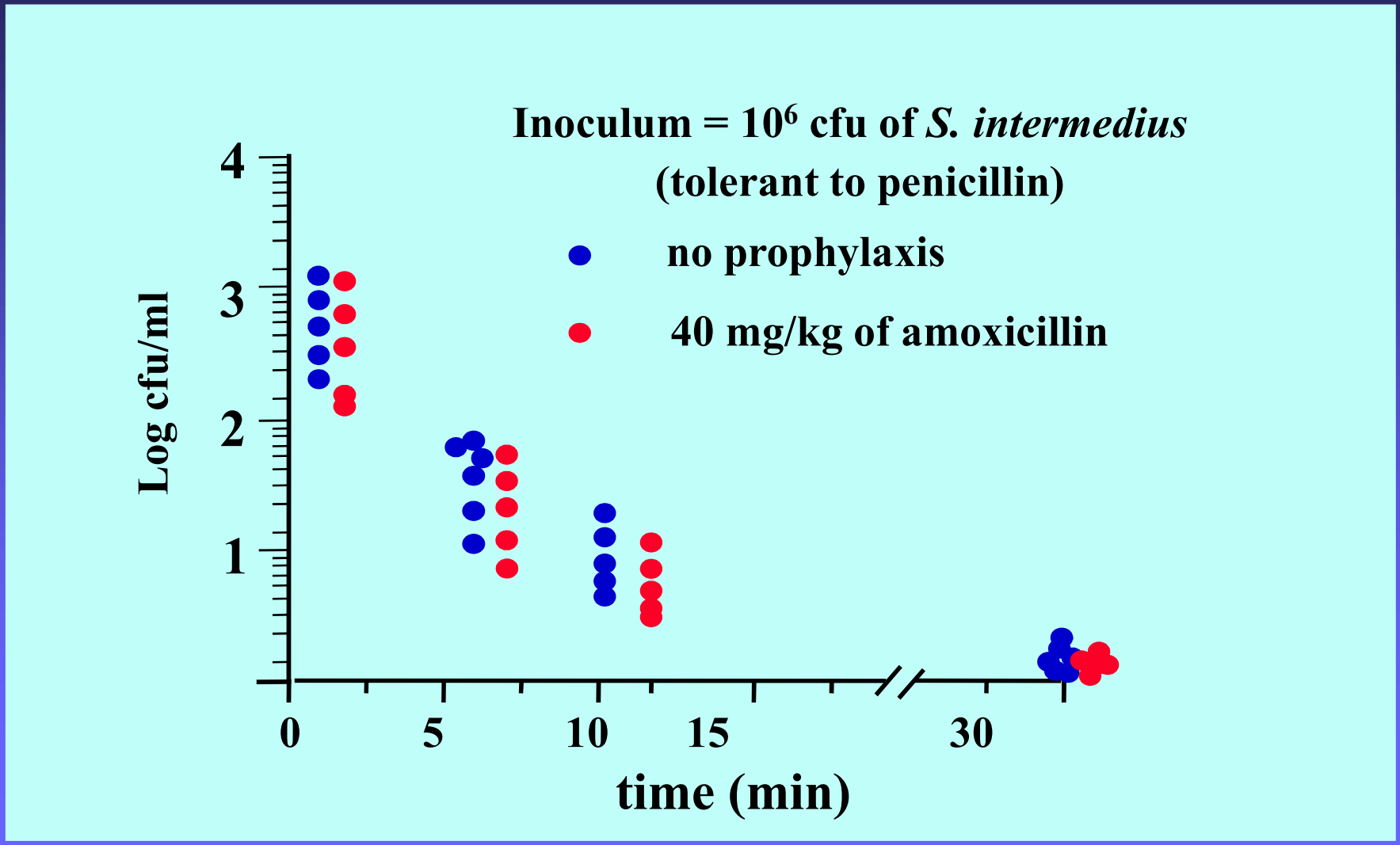




It works !!!

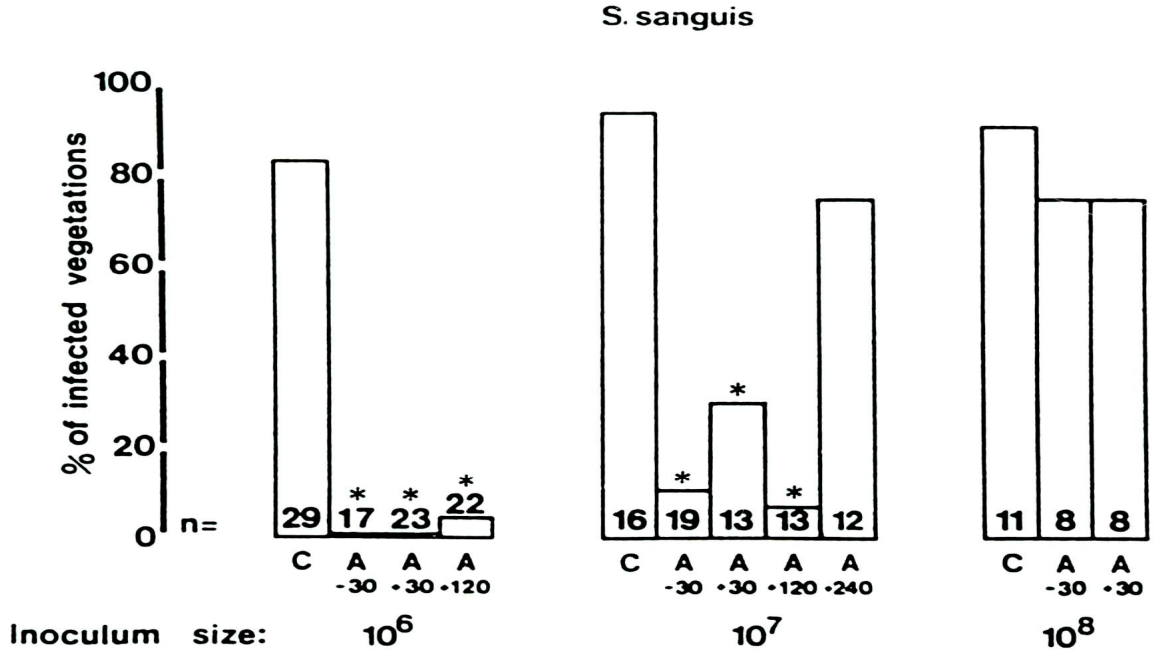
P Moreillon – UNI Lausanne

Bacteremia Following iv Inoculation of Rats Receiving or not Amoxicillin Prophylaxis



Experimental studies

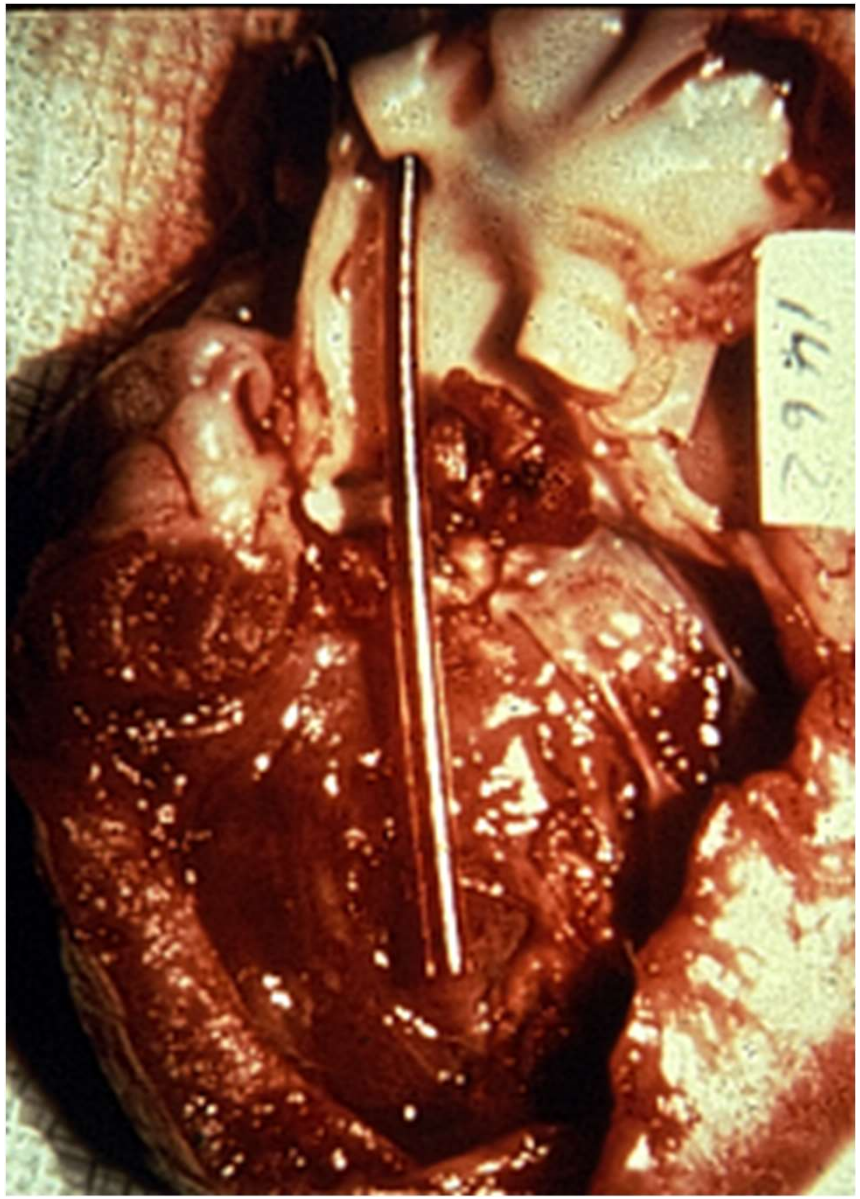
Amoxicillin before vs. after bacterial challenge



Incidence of endocarditis in control rats (C) and in rats given amoxicillin 30 min before (A−30) or 30–240 min after (A+30−A+240) bacterial challenge with various inocula of *S. sanguis*. *P* values were calculated by χ^2 analysis with Yates's correction; asterisk indicates $P < .05$ compared with controls. There were no significant statistical differences between A−30, A+30, and A+120.

Experimental Endocarditis

- Inoculum
- Bacteremia
- Drug kinetics
- Resistance



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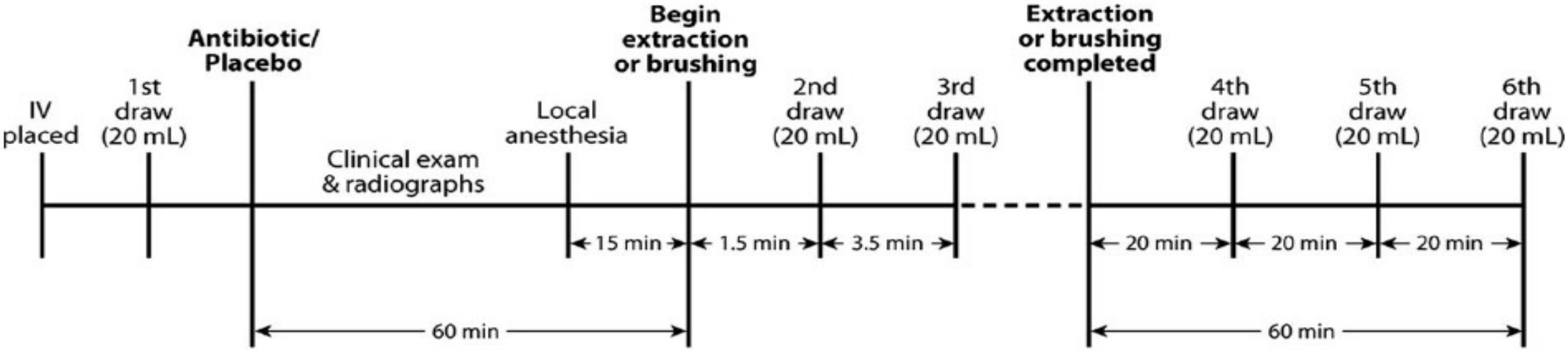
Bacteremia Associated With Toothbrushing and Dental Extraction

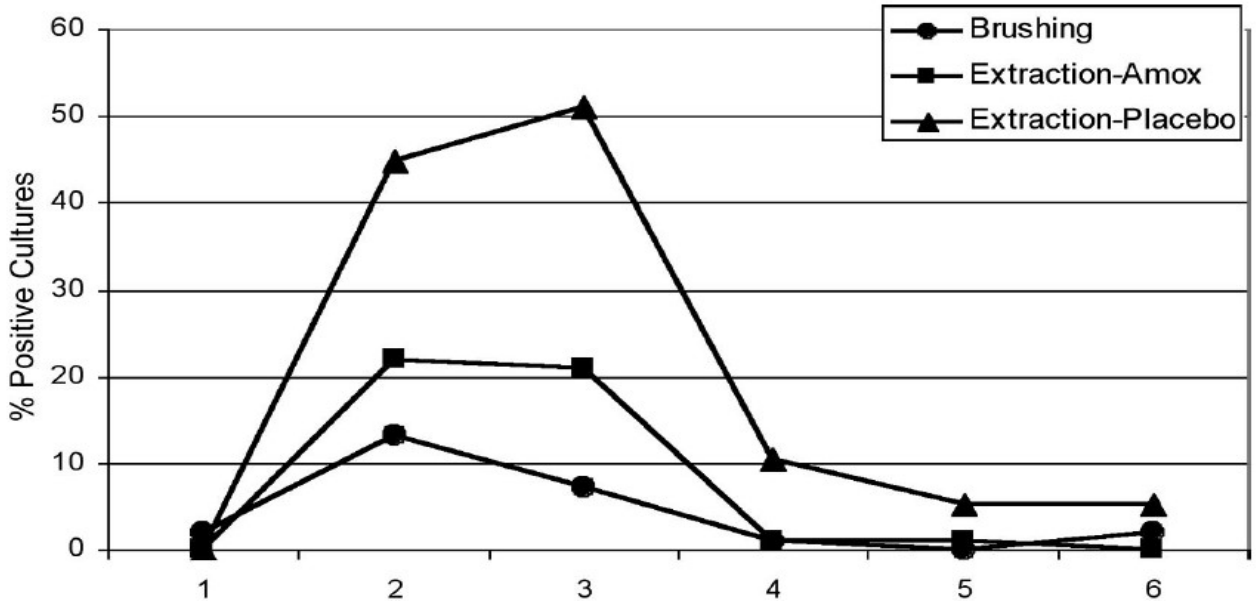
- Patients presented to urgent care service with the need for extraction of at least 1 erupted tooth
- Double-blind, placebo-controlled study
- Three randomization arms
  - Toothbrushing
  - single-tooth extraction with amoxicillin prophylaxis
  - single-tooth extraction with identical placebo



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

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*

2006 NIH R21 RCT Planning grant

Power calculations:

- Incidence of IE:
  - General population: ~2/100,000
  - Moderate risk population: ~20-30/100,000
  - High-risk population: ~300/100,000
- 12,000 high-risk patients would therefore only produce ~36 cases of IE
- <1/2 of IE cases caused by OVGS and therefore susceptible to AP = 18 cases
- When randomised = 9 cases on AP and 9 on placebo
- Assumes AP is 100% effective and none of the patients are edentulous

2006 NIH R21 RCT Planning grant

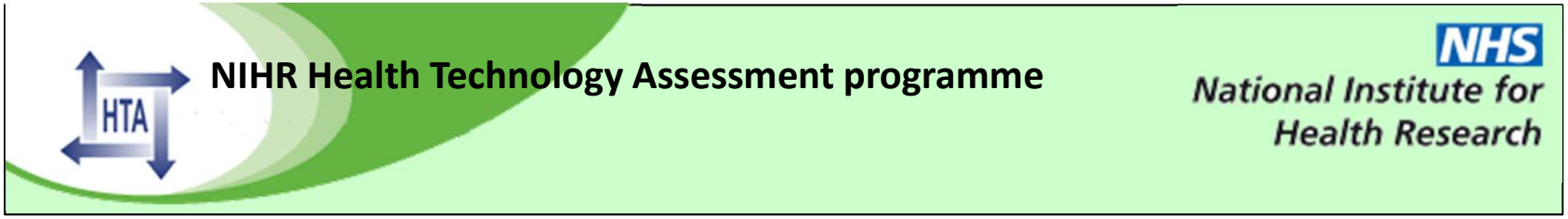
- Ethical/medico-legal issues randomising patients to placebo when AP is standard of care
- Moderate risk patients easier to recruit but because of lower risk of IE – much bigger numbers needed ~ 10 times more
- Cardiology units needed to identify and recruit high-risk patients
- But dentists also needed as they perform the procedures requiring AP cover
- Study is therefore very complex (expensive)

2011 NIHR HTA Grant Application

- We realised that the 2008 NICE guidance removed the ethical/medico-legal barriers to an RCT in the UK
- National data systems in the UK could help address size, complexity and cost issues
- We put together a multidisciplinary team of experts in IE and in complex clinical trial design (ScHARR and CTRU)

The APPROVED clinical trial

- A proposal for a double blind placebo controlled trial of 'Antibiotic Prophylaxis for the Prevention of PROsthetic Valve Endocarditis in Dentistry
- A UK wide collaborative study that would involve
  - All cardiothoracic centres in the UK
  - All primary and secondary care Dentists in the UK (CDOs)
  - Infectious Disease experts
  - Experts in Health Services Research, Health Economics and Clinical Trials Management.
- Grant application was submitted to:



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.

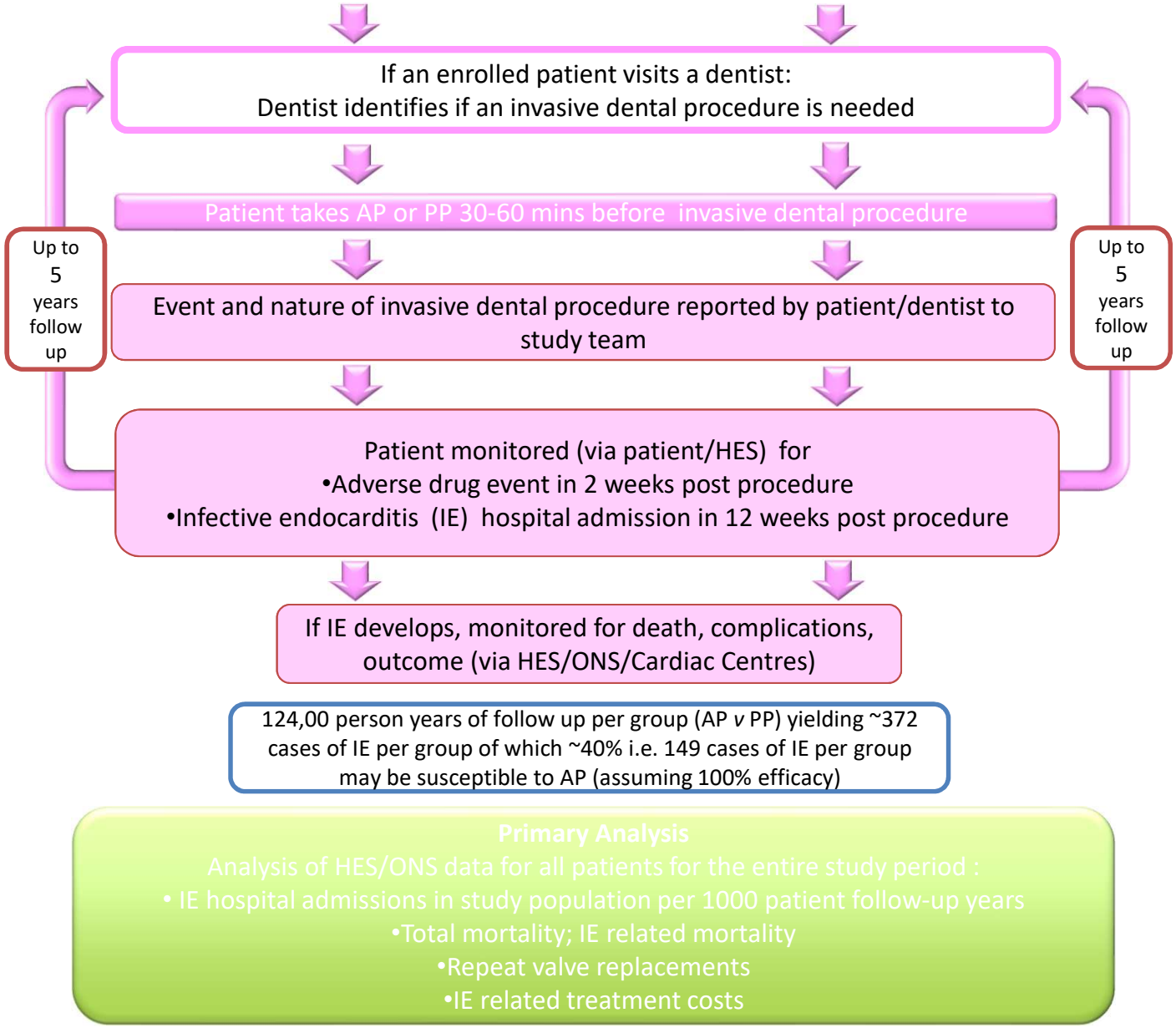
40,000 patients

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



The APPROVED clinical trial

NIHR – HTA

- Highly rated and recommended for funding
- Further funding assessment – estimated cost £12m (Euro 17m, US$ 19m)
- Too high a % of total NIHR research budget
  - Not justifiable for a relatively uncommon condition
  - Particularly in competition with much cheaper treatment RCTs for more common and equally serious diseases – cancer, diabetes, Alzheimer's etc
- NIHR commented that an RCT for IE unlikely to be fundable – recommended observational studies

The APPROVED clinical trial

- Took the APPROVED clinical trial to NIH (USA)
- NIH R34 – Clinical Trial Planning Grant
- Very impressed with the study design
- NIH decided they could consider the RCT even though it was to be performed entirely outside the USA
  - Because the ethical/medico-legal concerns could be overcome in the UK
  - Because the NHS and National data systems made the study possible and cheaper in the UK (not possible in USA)
- Because of the size of funding likely to be required – NIH put together a consortium of NHLI, NIDCR, NIAID to consider and fund it

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

Contributors

François Alla, Xavier Duval, 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

How could a registry-based randomized trial be implemented for AP of IE? Situation in France (2)

- Preliminary analyses from this database
  - 70,000 patients with prosthetic valves (identified since 2005)
  - Over a two-year period:
    - 94,000 dental interventions
    - 450 IE following these interventions
  - Rate of AP in PV carriers in whom AP is recommended: 45%

Possible study designs

- In countries where AP is recommended
  - Intervention: Actions to enforce AP according to existing guidelines (objective: reach ≥80% AP coverage rate)
  - Control: no intervention (i.e. expected AP coverage rate < 50%)
  - Randomization: Dentist?
  - Type of dental intervention: only high-risk
  - Type of at-risk patients: only high-risk
- In countries where AP is not recommended (UK, Sweden)
  - Intervention: AP according to pre-2008 guidelines
  - Control: no change (i.e. no AP, wherever NICE guidelines are enforced)
  - Randomization: geographic?
  - Type of dental intervention: any?
  - Type of at-risk patients: any at-risk or only high-risk?

Many questions

- Is an international collaboration possible when countries do not use the same health insurance system databases?
  - Yes (see European study on impact of screening on prostate cancer mortality)
  - National data and analyses are pooled, which increased the strength of the results
- Which endpoint and which analysis strategy?
  - Incidence of IE
  - Intent-to-prevent and per-prophylaxis
- Duration of exposure time frame?
- Management of PV subjects who undergo repeat at-risk procedures?
- New ethical issues
  - How and when inform patients? And obtain informed consent?
  - Would an informed consent be necessary in any case?
- ….

“Do what you can, with what you have, where you are.” Theodore Roosevelt

- The randomized registry trial represents a disruptive technology that will transform existing standards, procedures, and cost structures
- Will it be given serious consideration as a way to resolve the recognized limitations of current clinical trial design?
- Today we can no longer afford to undertake randomized effectiveness trials that cost tens or hundreds of millions of dollars.
- But today we have registries and other powerful digital platforms
- Today we must design and conduct megatrials with what we have: bigger data and smaller budgets

Adapted from Lauer and D'Agostino, NEJM 2103;369:1579)

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Is antibiotic prophylaxis effective? 3 case-control studies

- Imperiale, Am J Med 1990;88:131-6
  - 8 cases, 24 controls, dental procedures
  - Ab in 1/8 Ca vs. 15/24 Co (p=0,025),
  - OR=0.09 [0–0.99] – PE=91%
- Van der Meer, Lancet 1992;339:135-9
  - 48 cases, 200 controls, majority of dental procedures
  - Ab in 8/48 Ca vs. 28/200 Co (p=0.6)
  - OR=0.51 [0.1–2.3] – PE=49% (dental, within 30 days)
- Lacassin, Eur Heart J 1995;16:1968-74
  - 18 cases, 22 controls, dental procedures, dental IE
  - Ab in 3/18 Ca vs. 6/22 Co (p=0,4)
  - OR=0.54 [0.1-3.1] – PE=46%

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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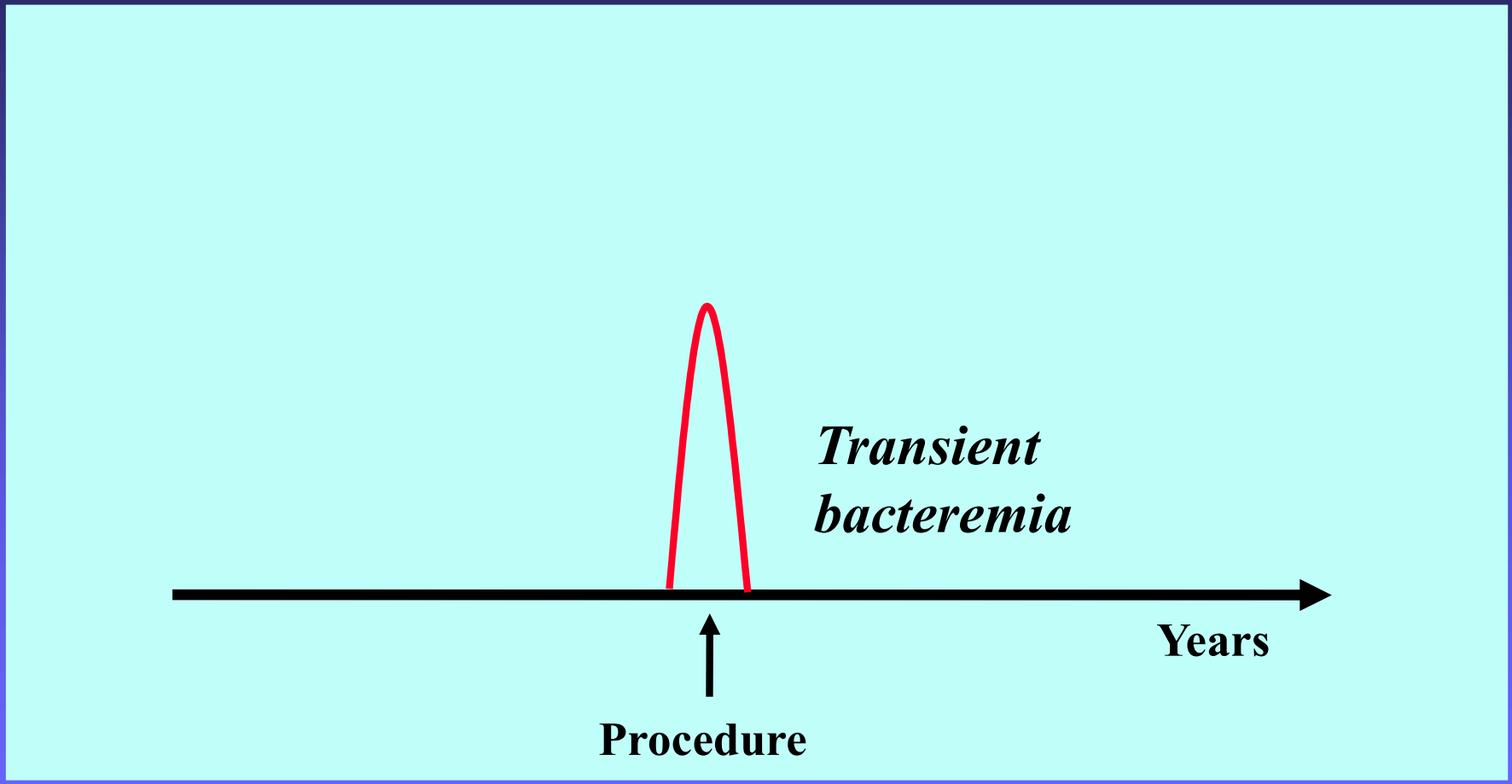
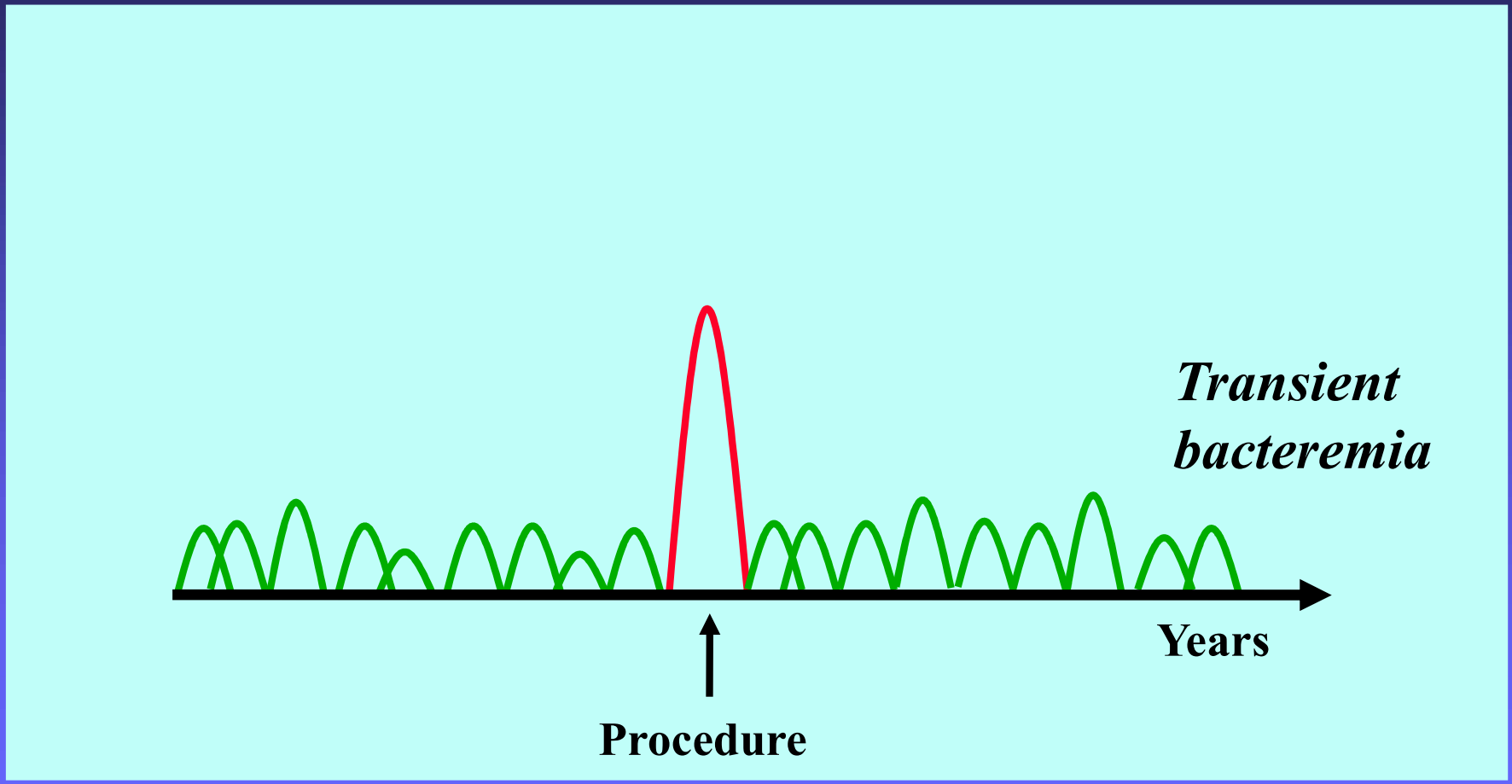
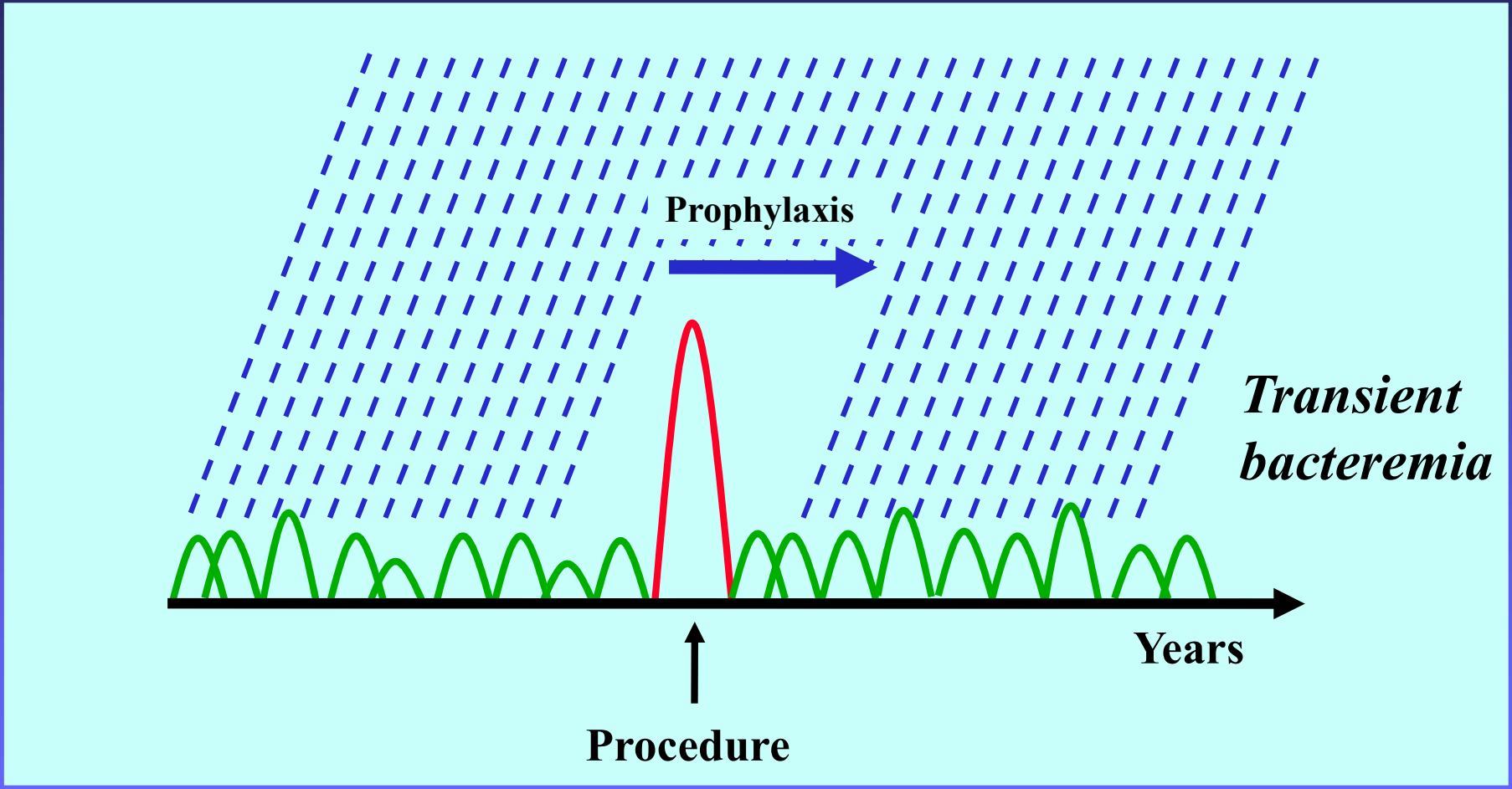
Procedure-induced Bacteremia



Overall Transient Bacteremia

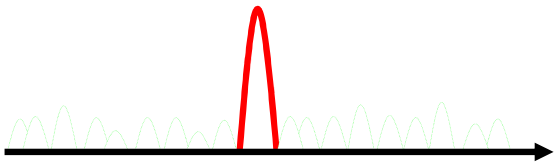


Limited Effect of Antibiotic Prophylaxis

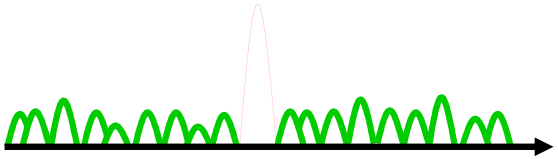


Cumulative bacteremia and risk of IE in a rat model

SAME INOCULUM

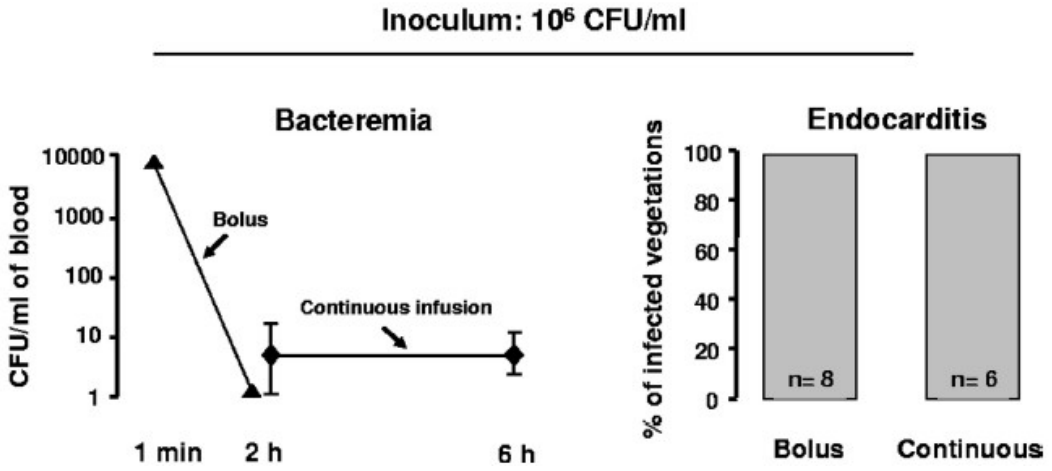


Bolus
1 ml / 1 min



Continuous infusion
0,0017 ml/min over 10 h

S. gordonii



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

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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

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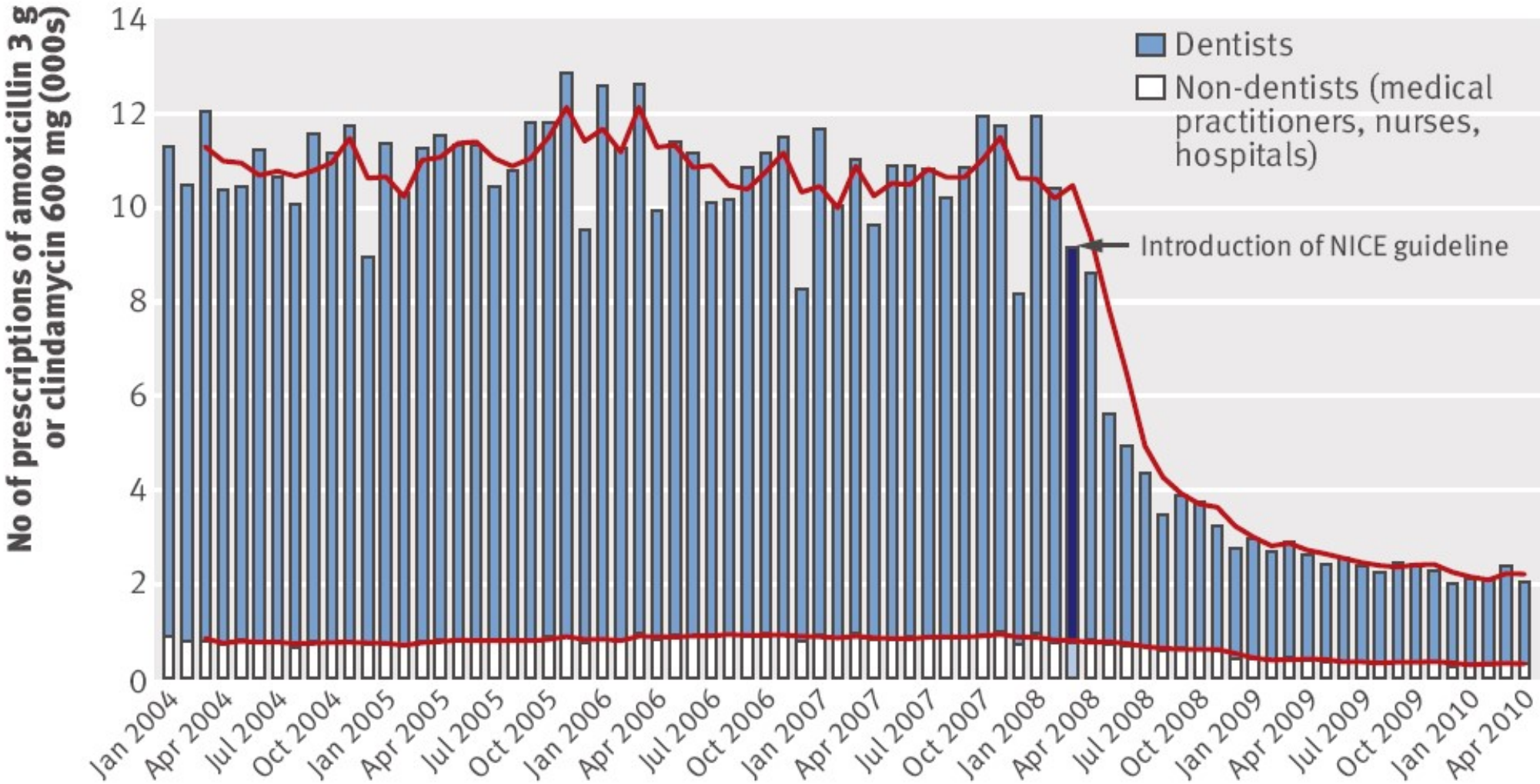
Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of IE



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

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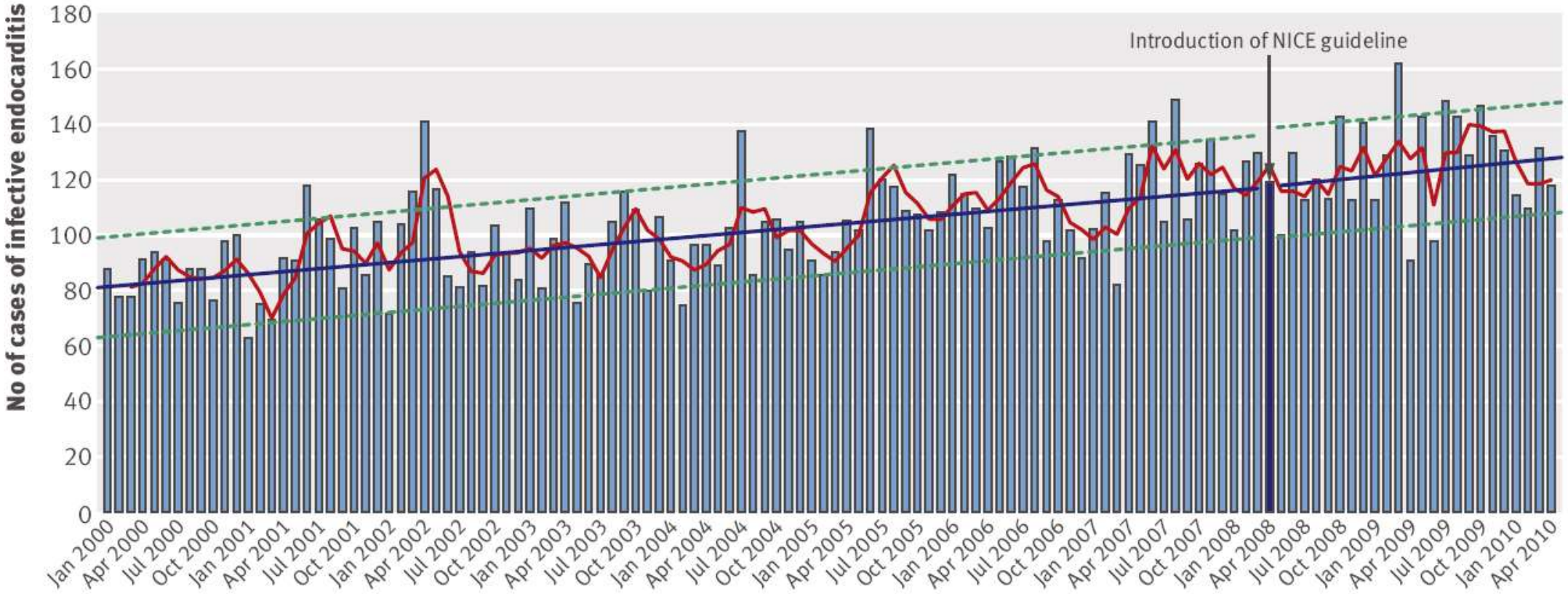

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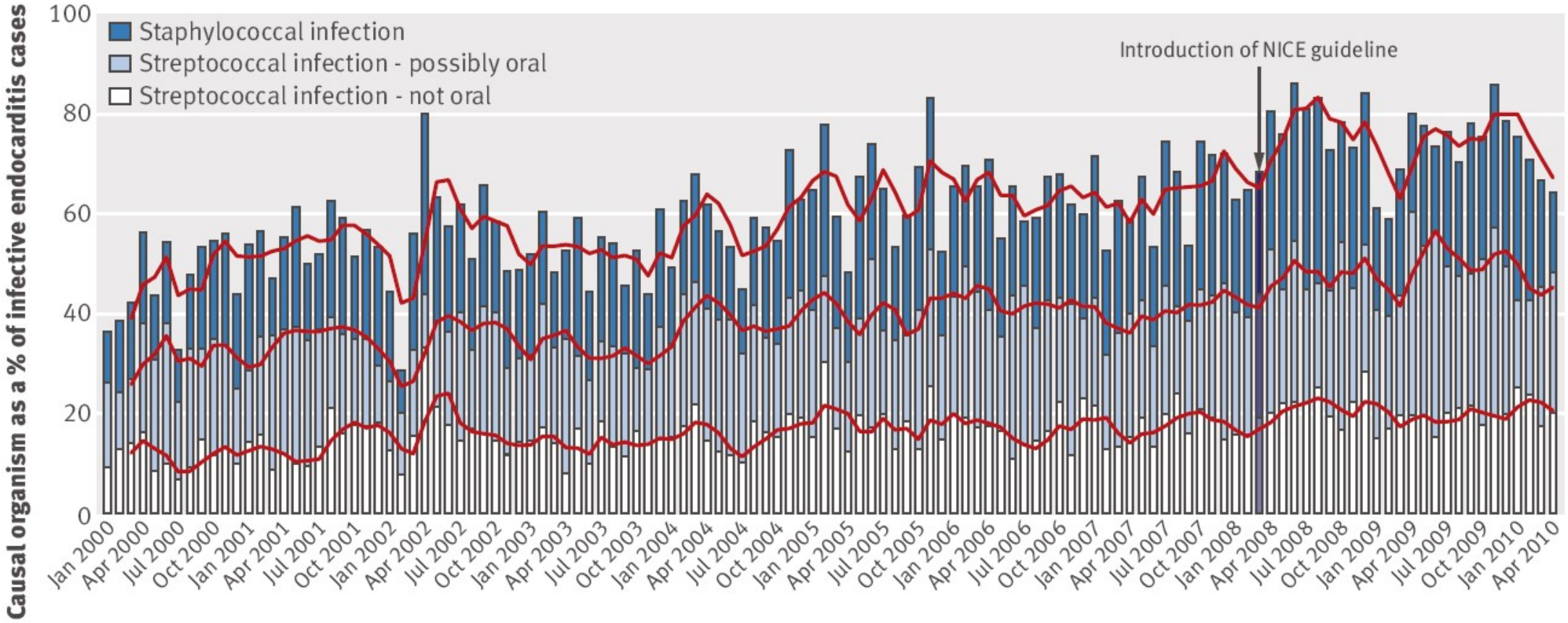

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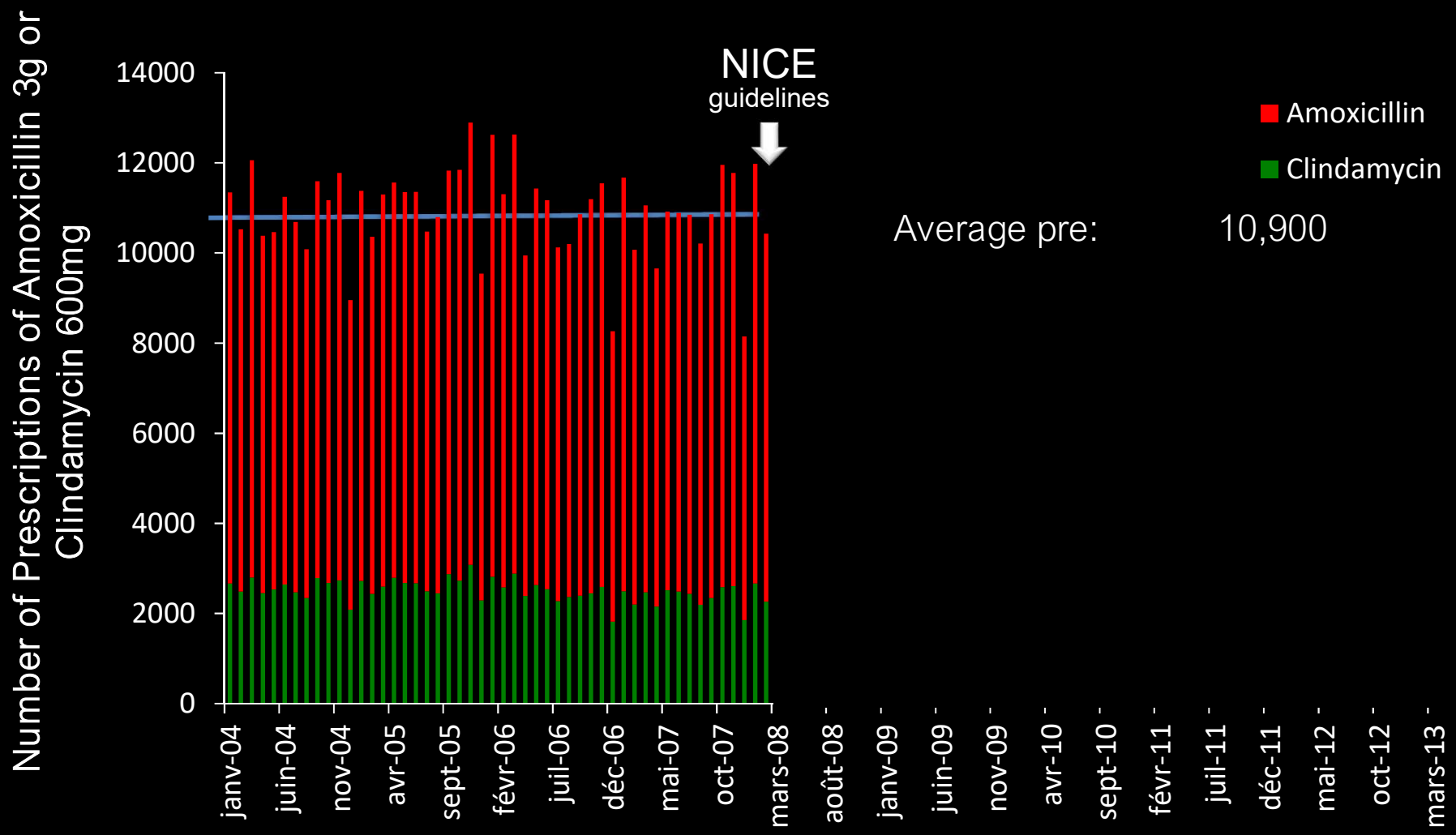
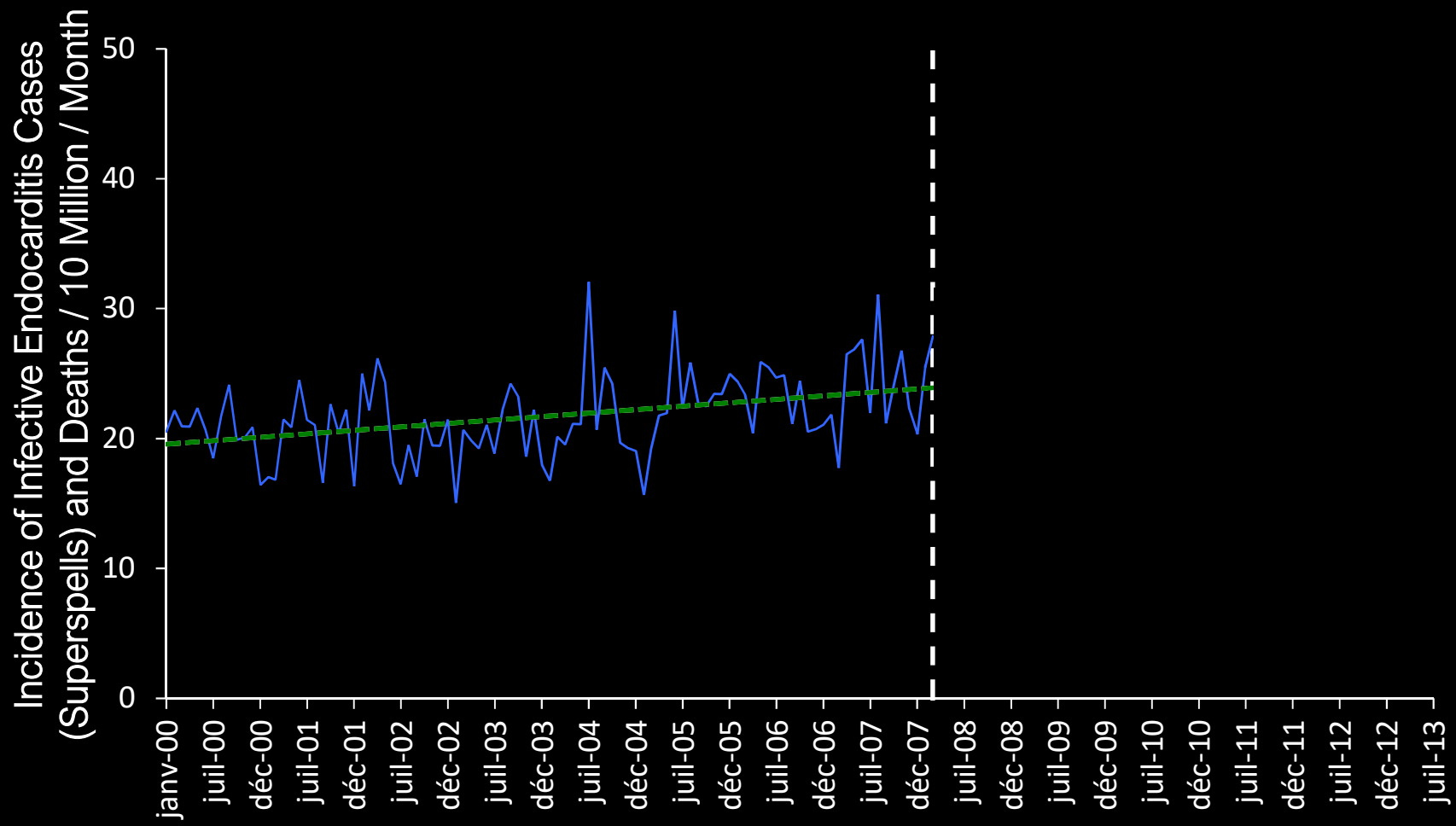
Antibiotic Prophylaxis Prescribing Data



Dayer M, Lancet 2015;395:1219

Incidence of IE



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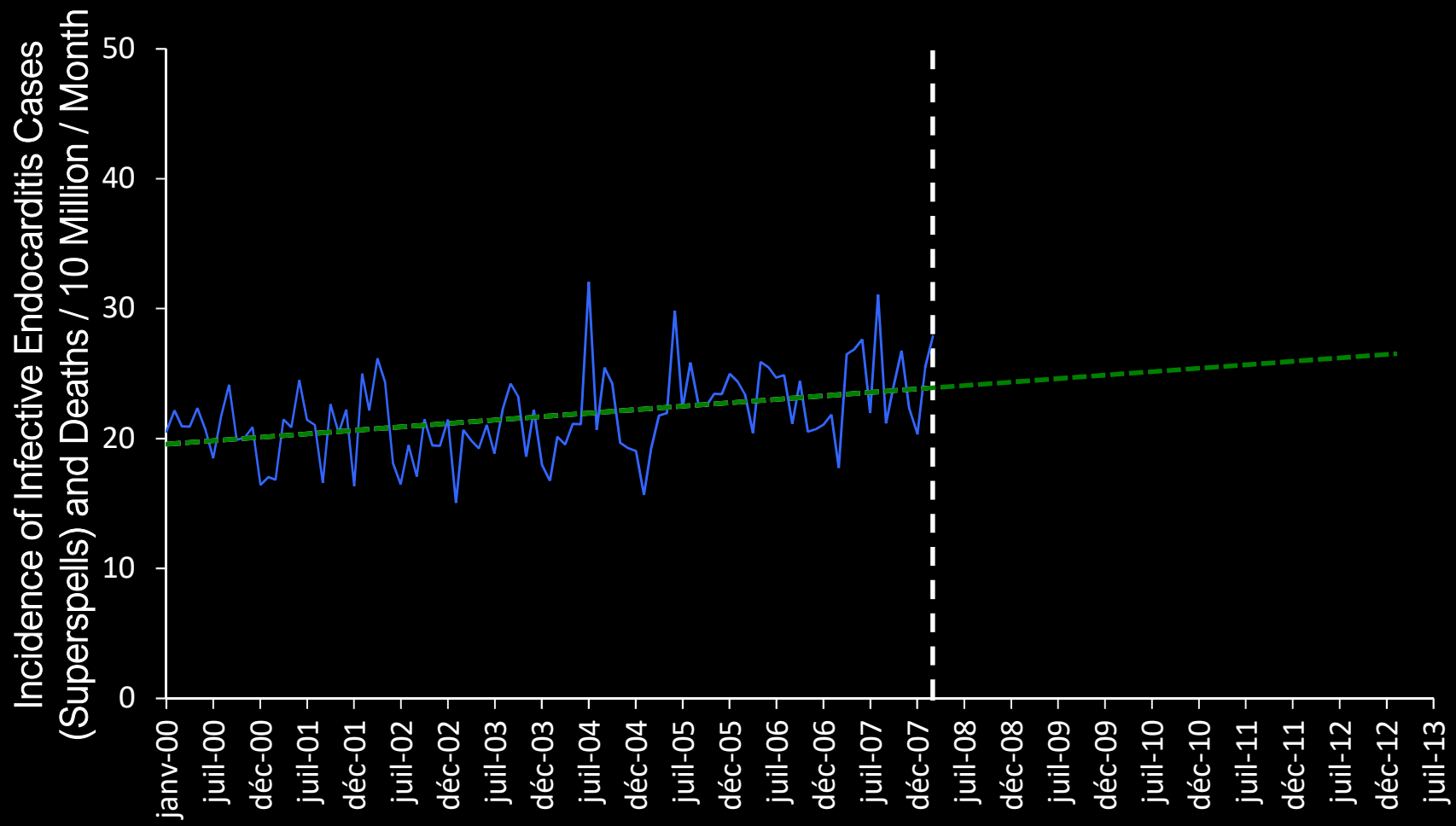

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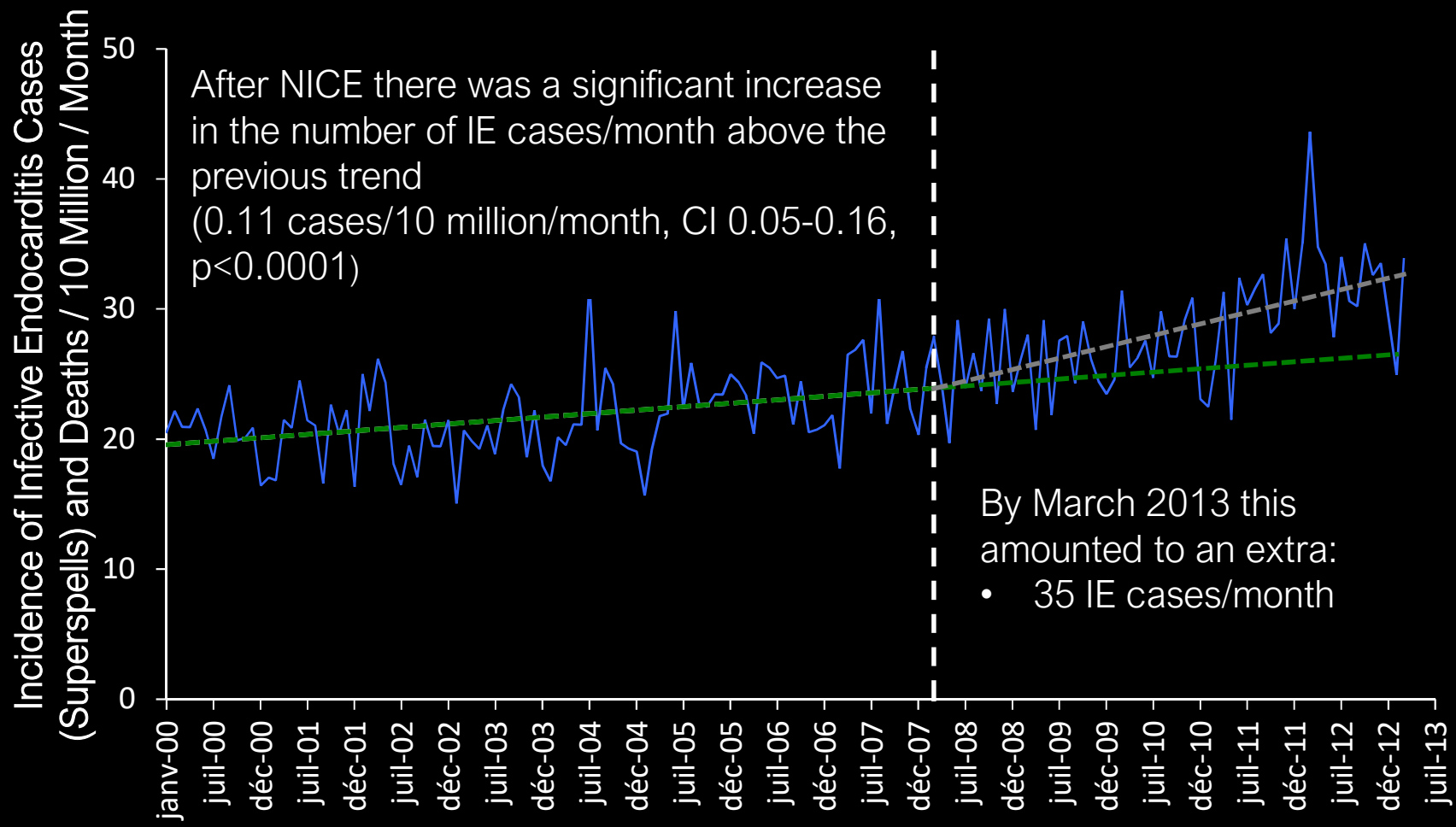
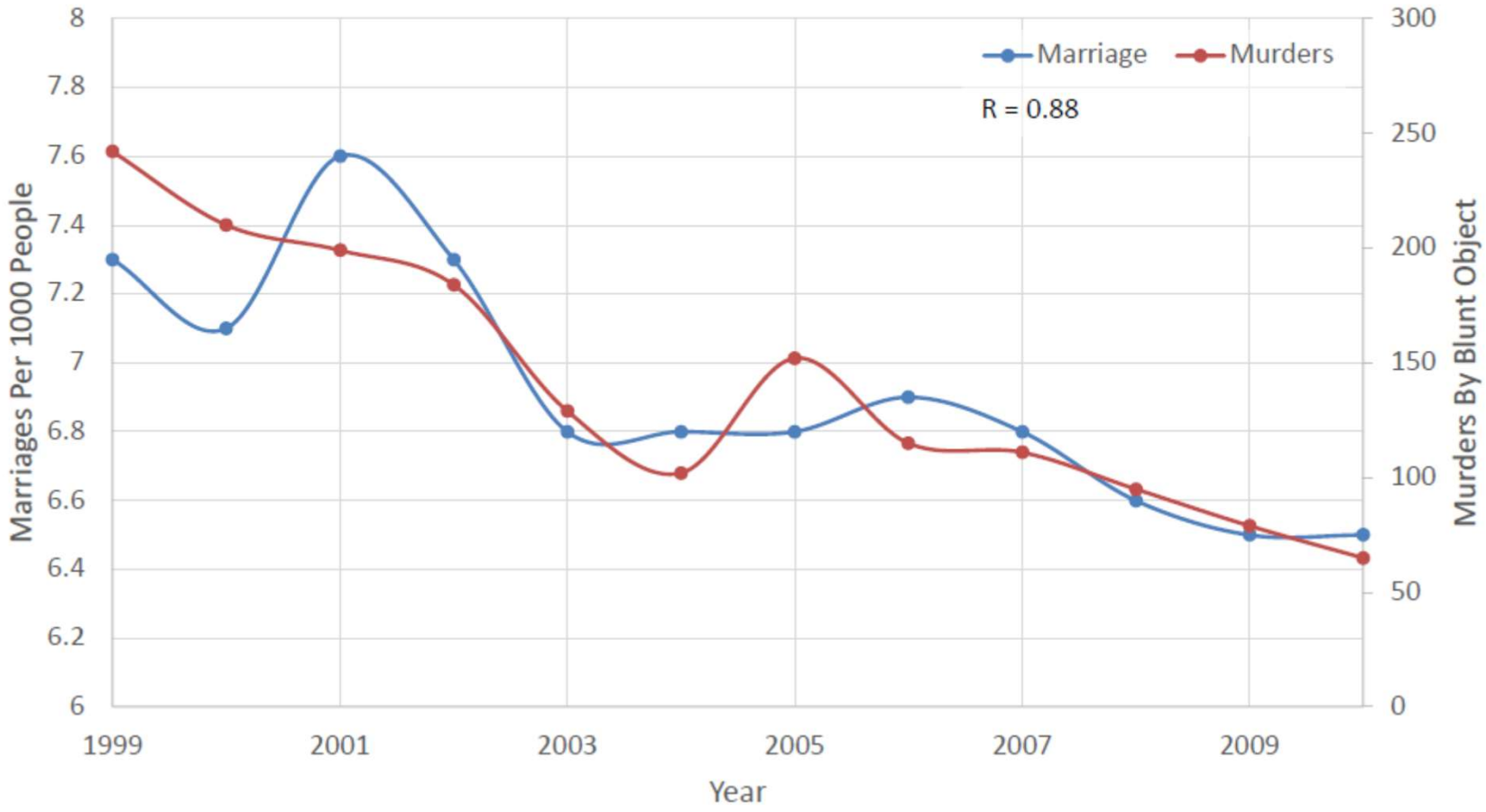


Dayer M, Lancet 2015;395:1219

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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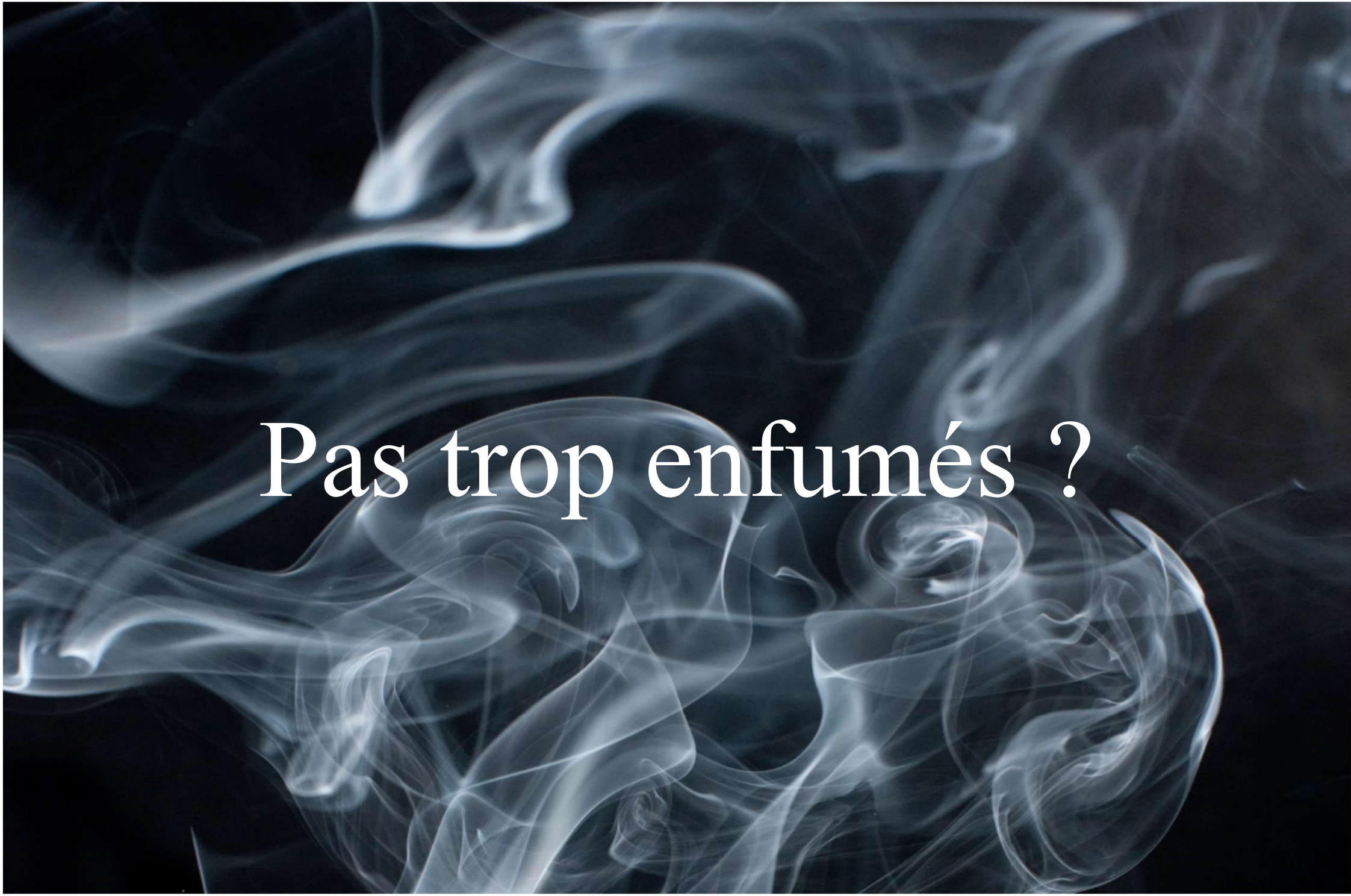
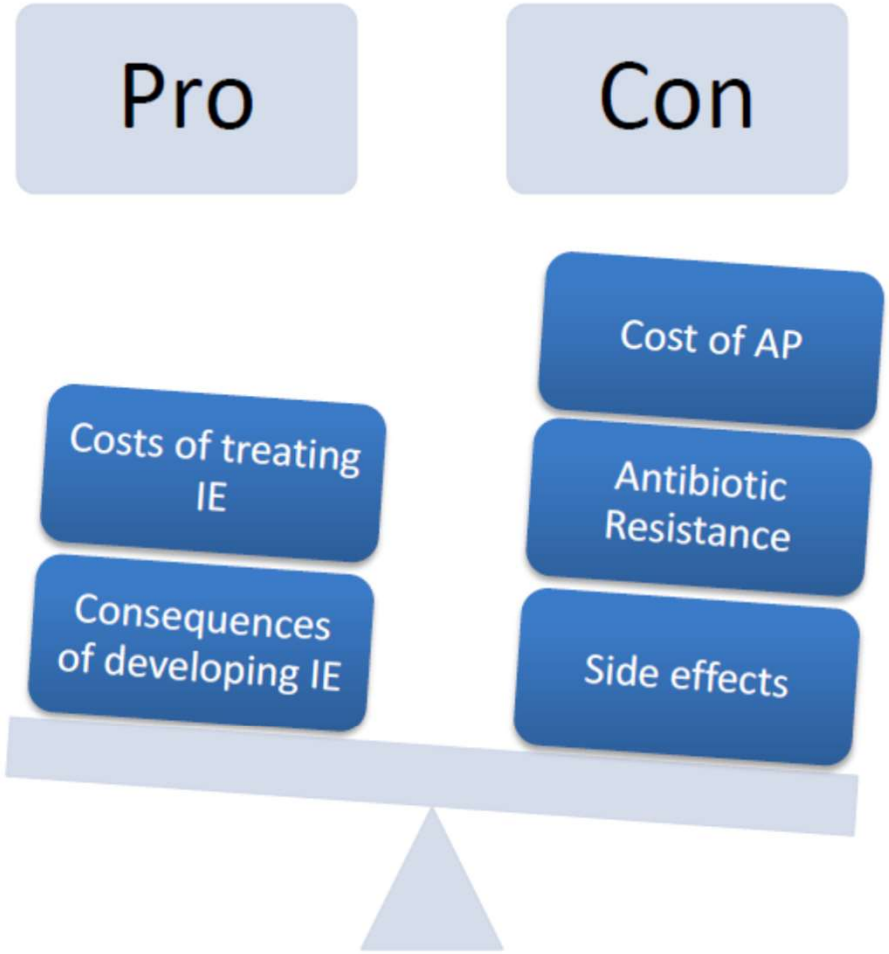

Pas trop enfumés ?

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 cards (1)

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

CONSEILS PENDANT LA DURÉE DU TRAITEMENT ANTICOAGULANT

SFC
SFCTCV

Traitement : ❑ Temporaire ❑ Définitif

INR CIBLE : entre ..... et ..... Contrôlez l'INR au moins une fois par mois

Notez les INR sur votre carnet de traitement anticoagulant

- Ne prenez aucun autre médicament sans avis médical (risques d'interactions)
- Consultez votre médecin en urgence en cas de saignement ou d'hématome ou si l'INR est supérieur à 5
- Prenez l'avis de votre médecin si l'INR est en dehors des valeurs cibles
- Signalez que vous êtes sous anticoagulant à tout médecin/professionnel de santé
- Ne modifiez pas ou n'interrompez pas le traitement sans avis médical

Cardiologue traitant ..... Médecin traitant .....

Fédération Française de Cardiologie

SPILF
SFC / FFC
SFCTCV ADF

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IE prophylaxis cards (2)

SPILF
FFC / SFC,
SFCTCV ADF

PRÉVENTION DE L'ENDOCARDITE INFECTIEUSE

Actualisation 2011 des recommandations

Nom, prénom : .....

Vous présentez la cardiopathie suivante :

- ❑ Insuffisance aortique, insuffisance mitrale, rétrécissement aortique, bicuspidie aortique
- ❑ Cardiopathie congénitale non cyanogène
- ❑ Prolapsus valvulaire mitral avec insuffisance mitrale / épaississement
- ❑ Cardiomyopathie hypertrophique obstructive

Cette cardiopathie peut être associée à la survenue d'une endocardite infectieuse. Elle ne justifie toutefois pas l'administration préventive d'antibiotiques avant un soin dentaire.

Remis par le Dr : .....

le : ..... à : .....

tél. : ..... email : .....

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

Prophylaxis of IE: beyond antibiotic prophylaxis

- Oral hygiene
- Prevention of healthcare-associated IE
  - Prevention of healthcare-acquired bacteremia. Reducing the rate of central line-associated bloodstream infections can be achieved by practice-changing interventions
  - Prevention of IE associated with cardiac implantable electronic devices
- Innovative approaches
  - Inhibition of bacterial adhesion to
    - living surfaces (endocardium)
    - inert surfaces (prostheses, endovascular/intracardiac devices)
  - Vaccination
    - *S. aureus, P. aeruginosa, S. agalactiae*

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Clinical Infectious Diseases

MAJOR ARTICLE

Oral Streptococcal Endocarditis, Oral Hygiene Habits, and Recent Dental Procedures: A Case-Control Study

Xavier Duval,[1] Sarah Millot,[2] Catherine Chirouze,[3,a] Christine Selton-Suty,[4,a] Vanessa Moby,[5,a] Pierre Tattevin,[6] Christophe Strady,[7] Edouard Euvrard,[8] Nelly Agrinier,[9] Daniel Thomas,[10] Bruno Hoen,[11,b] and François Alla,[12,b]; for the EI-dents Association pour l'Etude et la Prévention de l'Endocardite Infectieuse (AEPEI) Study Group

[1]Inserm CIC-1425, AP-HP, Hôpital Universitaire Bichat; Inserm UMR-1137 IAME; Université Paris Diderot, UFR de Médecine-Bichat, and [2]UMR 1149-Inserm, CRI, Université Paris Diderot, Faculté de médecine Bichat, Paris; [3]UMR 6249 Laboratoire Chrono-environnement Université de Bourgogne Franche-Comté, Service de maladies infectieuses, CHRU Besançon; [4]Centre Hospitalier Régional Universitaire, and [5]Service Odontologie–Centre Hospitalier Régional Universitaire Nancy; [6]Maladies Infectieuses et Réanimation Médicale, Centre Hospitalier Universitaire, Rennes, [7]Cabinet d'infectiologie, Clinique Saint André-Groupe Courlancy, Reims, [8]Inserm, CIC-1431; Service de Stomatologie, Chirurgie Maxillofaciale et Odontologie Hospitalière, CHRU Besançon; [9]Inserm, CIC-1433 Epidémiologie Clinique, Centre Hospitalier Régional Universitaire, Nancy; [10]AP-HP, Hôpital Pitié-Salpêtrière, Département de Cardiologie, Paris; [11]Université des Antilles et de la Guyane, Faculté de Médecine Hyacinthe Bastaraud, EA 4537; Centre Hospitalier Universitaire de Pointe-à-Pitre, Inserm CIC-1424, Service de Maladies Infectieuses et Tropicales, Dermatologie, Médecine Interne, Pointe-à-Pitre; and [12]Université de Lorraine, Université Paris Descartes, Apemac, EA4360; Inserm, CIC-1433, Nancy, France

Clinical Infectious Diseases 2017;64(12):1678–85

Oral hygiene and dental procedures

	Whole population		Case-patients		Control-patients		
	274		73 (26·6%)		201 (73·4%)		
	N	%	N	%	N	%	p
Patient self-reported oral hygiene							
Tooth brushing frequency							0.6780
More than twice daily	37	16.2	9	13.6	28	17.3	
Twice daily	88	38.6	28	42.4	60	37.0	
Once daily	67	29.4	20	30.3	47	29.0	
Less than once daily	22	9.6	7	10.6	15	9.3	
Tooth brushing after meals	126	53.6	30	44.8	96	57.1	0.0500

Oral hygiene and dental procedures

Whole population		Case-patients		Control-patients		
274		73 (26·6%)		201 (73·4%)		
N	%	**N**	**%**	**N**	**%**	p
Toothpicks use	67	29.6	24	**36.9**	**43**	**26.7**	0.1913
Water pik use	10	4.4	5	**7.6**	**5**	**3.1**	0.1775
Flossing	19	8.3	11	**16.7**	**8**	**4.9**	0.0083
Interdental brush	24	10.7	9	**14.1**	**15**	**9.3**	0.3093

Oral hygiene and dental procedures

	Whole population		Case-patients		Control-patients		
	274		73 (26·6%)		201 (73·4%)		
	N	%	N	%	N	%	p
Toothpicks use	67	29.6	24	36.9	43	26.7	0.1913
Water pik use	10	4.4	5	7.6	5	3.1	0.1775
Flossing	19	8.3	11	16.7	8	4.9	0.0083
Interdental brush	24	10.7	9	14.1	15	9.3	0.3093
At least one of these behaviours	93	40.1	37	**55.2**	56	33.9	0.0091

Multivariate analysis

Factor associated with oral streptococci IE

	OR	95% CI	p
Age < 65 years	**2.50**	(1.25-5.00)	**0.0095**
Female	**2.25**	(1.05-4.80)	**0.0366**
Native valve diseases	**2.43**	(1.17-5.05)	**0.0411**
Pulpal necrosis	3.36	(0.61- 9.69)	**NS**
No interdental manipulations			
and tooth brushing after meals	**1**		**0.0005**
Without tooth brushing after meals	**5.29**	(2.00- 14.02)	
Interdental manipulations			
and tooth brushing after meals	**3.60**	(1.35-9.57)	
Without tooth brushing after meals	**6.40**	(2.17-18.85)	
Dental invasive procedures within the 3 preceding months	**3.49**	(1.26-9.69)	**0.0166**

Prophylaxis of IE: beyond antibiotic prophylaxis

- Oral hygiene
- Prevention of healthcare-associated IE
  - Prevention of healthcare-acquired bacteremia. Reducing the rate of central line-associated bloodstream infections can be achieved by practice-changing interventions
  - Prevention of IE associated with cardiac implantable electronic devices
- Innovative approaches
  - Inhibition of bacterial adhesion to
    - living surfaces (endocardium)
    - inert surfaces (prostheses, endovascular/intracardiac devices)
  - Vaccination
    - *S. aureus, P. aeruginosa, S. agalactiae*

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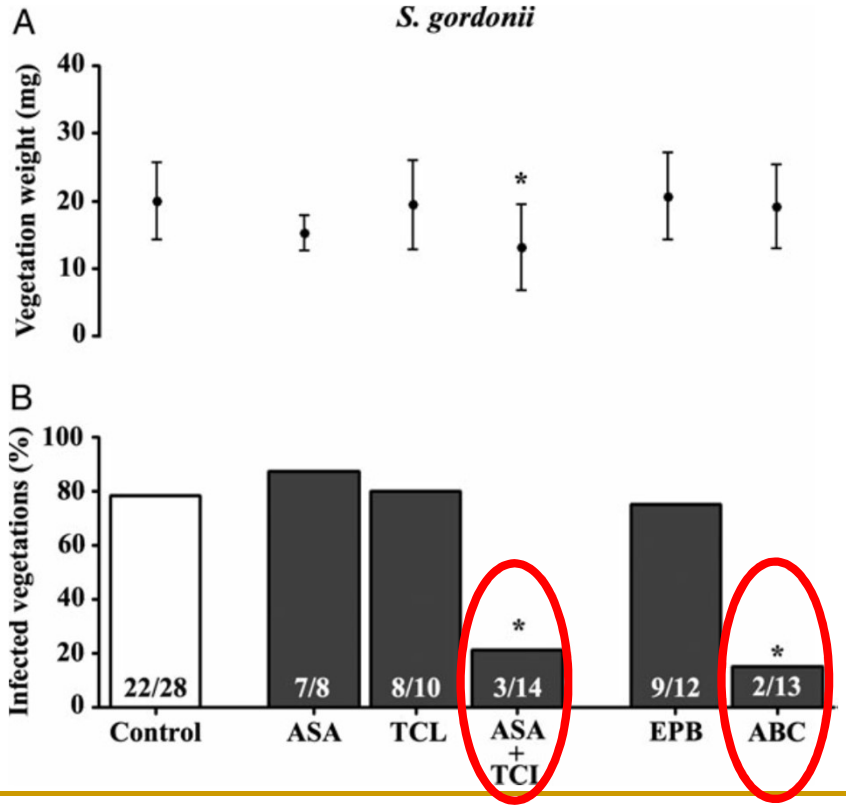
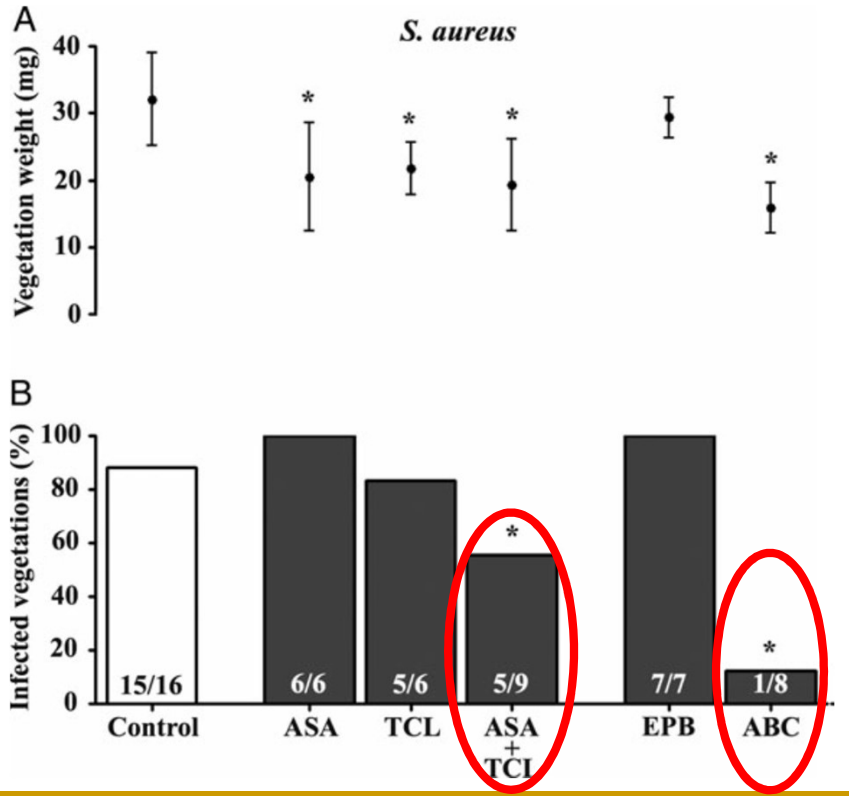
Prophylaxis of experimental IE with Antiplatelet and Antithrombin Agents (1)

- Rat model of experimental IE following prolonged low-grade bacteremia mimicking smoldering bacteremia in humans

APA



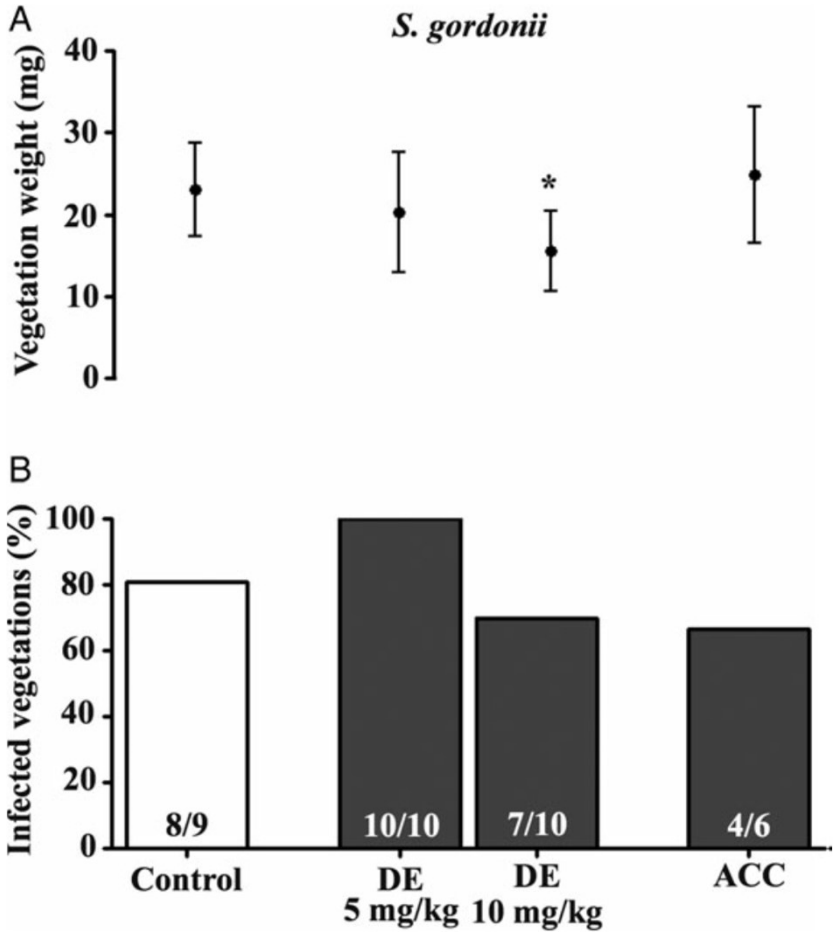


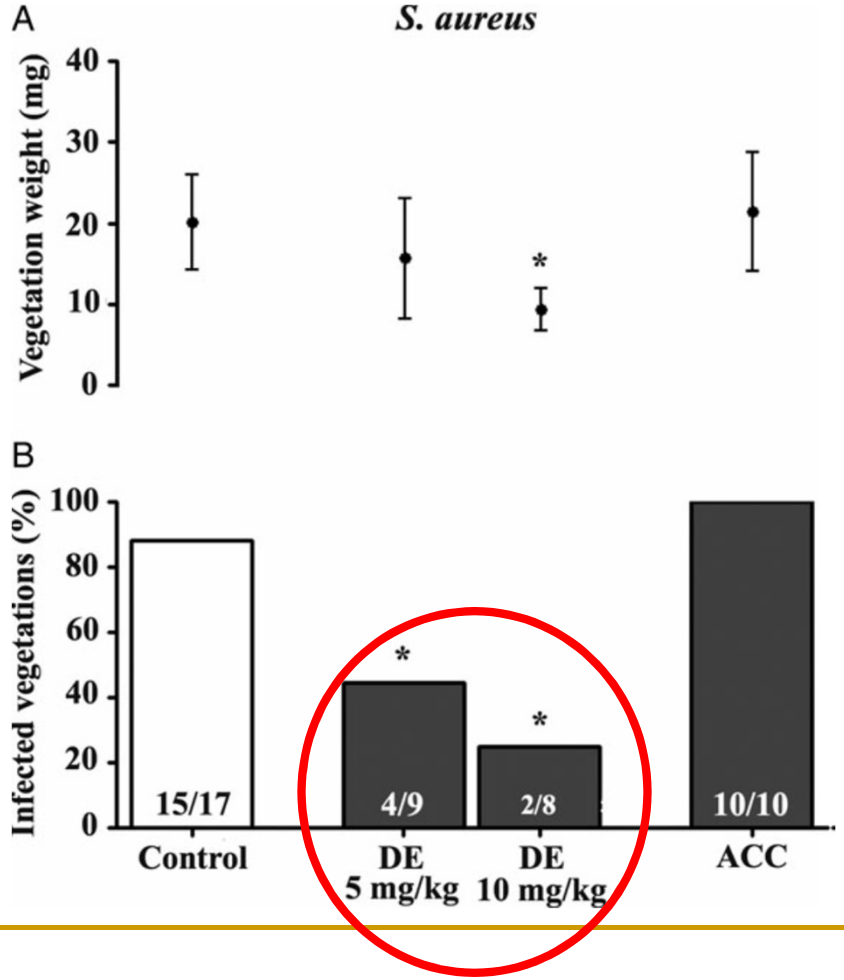
ASA : aspirin, TCL ticlopidine, EPB : eptifibatide, ABC : abciximab

Veloso TR, J Infect Dis 2015;211:72–9

Prophylaxis of experimental IE with Antiplatelet and Antithrombin Agents (2)

ATA





DE : dabigatran etexilate, ACC : acenocoumarol

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Thank you for your attention