Convegno Nazionale
Microbiologia Clinica e Infettivologia:
una combinazione sinergica per una nuova realtà sanitaria

Clostridium difficile: terapia eziologica e preventiva

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Ospedale di Cremona
Sistema Socio Sanitario
Regione Lombardia
ASST Cremona

Conflitti di interesse

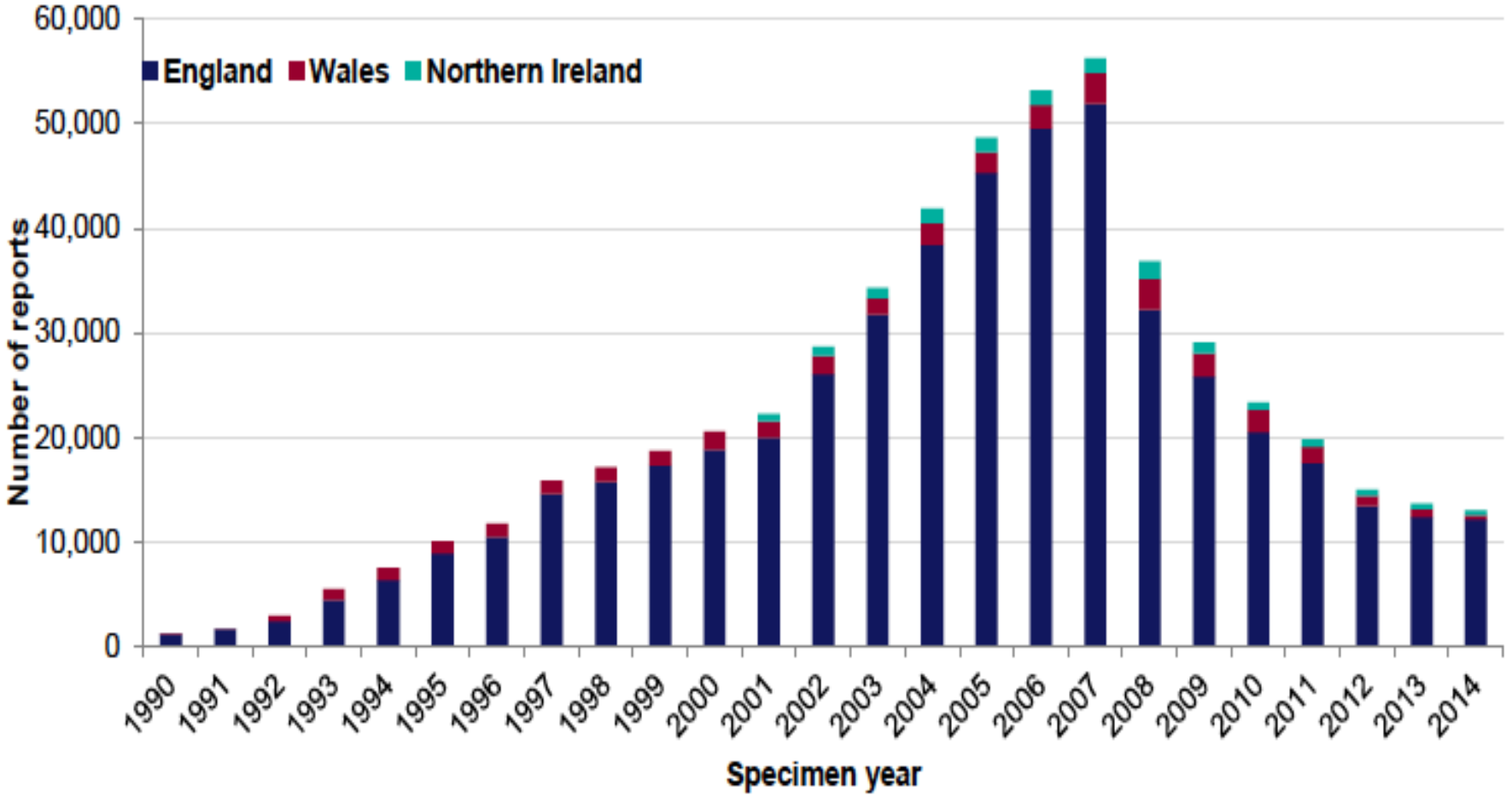
- Progetti: CCM, SIMIT
- Relazioni a congressi: Pfizer
- Partecipazione a congressi: Angelini, Jannsen, Merck, ViiV

- Introduzione
- Terapia
- Prevenzione
- Un’esperienza personale
- Conclusioni

- **Introduzione**
- Terapia
- Prevenzione
- Un’esperienza personale
- Conclusioni

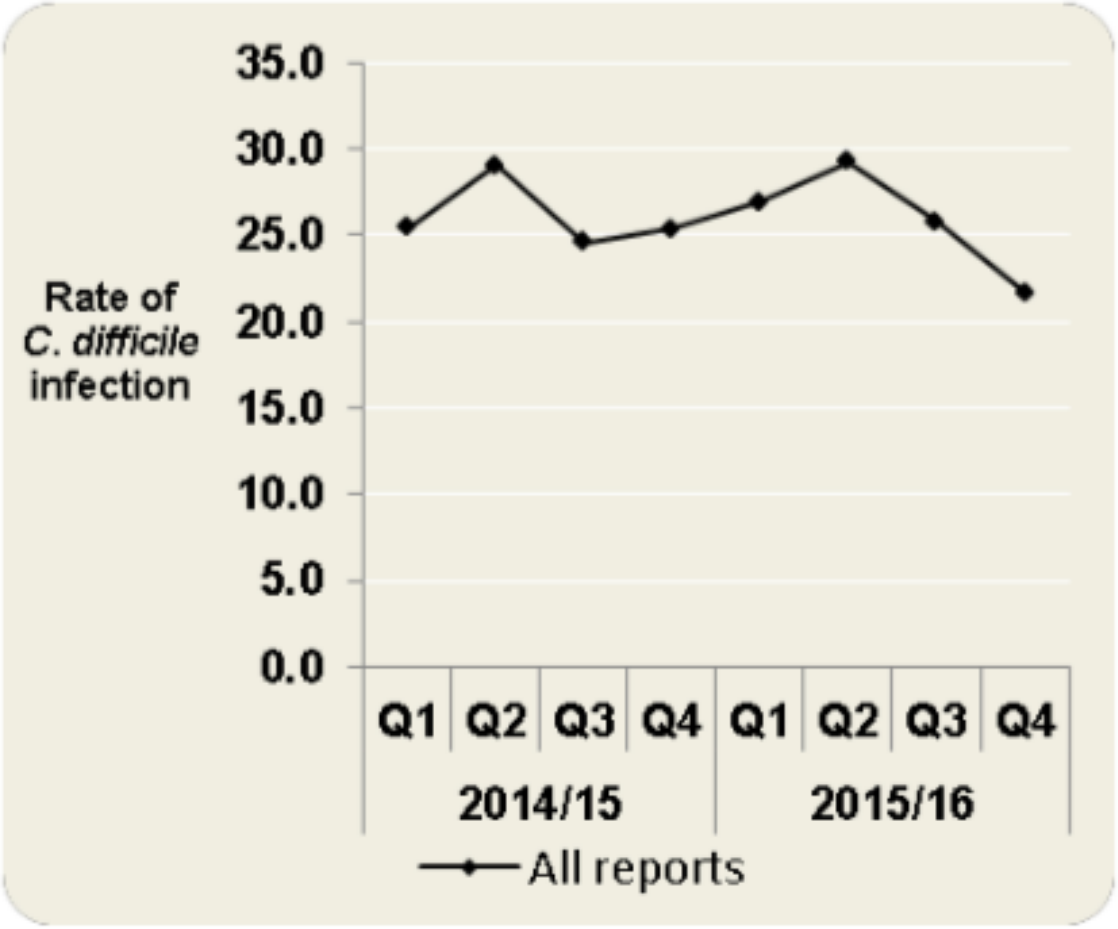
Piero Manzoni, 1961

Epidemiologia – Regno Unito



Health Protection Report Vol 9 No. 21 – 19 June 2015

Epidemiologia – Regno Unito



Quarterly epidemiological commentary, 2016

- Introduzione
- **Terapia**
- Prevenzione
- Un’esperienza personale
- Conclusioni

Quale terapia?

- Quale paziente??
- Definire la gravità

Stadiazione della gravità

1–3 Points, Mild to Moderate Disease; 4–6 Points, Severe Disease; ≥7 Points, Severe Complicated Disease	
Criteria	**Points**
Immunosuppression and/or chronic medical condition	1
Abdominal pain and/or distention	1
Hypoalbuminemia (<3 g/dL)	1
Fever (>38.5°C)	1
ICU admission	1
CT scan with nonspecific findings of pancolitis, ascites, and/or bowel wall thickening	2
WBC count > 15,000 or <1.500 and/or band count > 10%	2
Creatinine 1.5-fold > baseline	2
Abdominal peritoneal signs	3
Vasopressors required	5
Mechanical ventilation required attributed to CDAD	5
Disorientation, confusion, or decreased consciousness	5

*This scoring system is for patients with a diagnosis of CDAD and is not yet validated.
CDAD: Clostridium difficile associated disease.

1-3 punti: lieve – moderato

4-6 punti: grave

≥7 punti: grave complicato

Variable	Odds Ratio	95% Confidence Interval	Points
Age > 70 y	3.80	1.14–13.68	2
WBC count ≥ 20,000/μL or ≤2,000/μL	1.81	0.54–6.05	1
Cardiorespiratory failure*	285	24–21,491	7
Diffuse abdominal tenderness	189	27–8,429	6

*Cardiorespiratory failure: the need for mechanical ventilation or vasopressor support.

≥6 punti: grave

Neal, Ann Surg 2011; van der Wilden, J Trauma Acute Care Surg 2014

Cochrane Library

Cochrane Database of Systematic Reviews

Sospensione del trattamento iniziale

Antibiotic treatment for Clostridium difficile associated diarrhea in adults (Review)

Nelson RL, Kelsey P, Leeman H, Meardon N, Patel H, Paul K, Rees R, Taylor B, Wood E, Malakun R

Efficacia 15%

Usata un tempo

Analysis 1.1. Comparison 1 Vancomycin versus Placebo, Outcome 1 Symptomatic Initial Response.

Review: Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults

Comparison: 1 Vancomycin versus Placebo

Outcome: 1 Symptomatic Initial Response

Study or subgroup	Vancomycin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Keighley 1978	9/22	1/22			9.00 [1.24, 65.16]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**

Total events: 9 (Vancomycin), 1 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Placebo Vancomycin

Analysis 1.2. Comparison 1 Vancomycin versus Placebo, Outcome 2 Bacteriologic Initial Response.

Review: Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults

Comparison: 1 Vancomycin versus Placebo

Outcome: 2 Bacteriologic Initial Response

Study or subgroup	Vancomycin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Keighley 1978	10/22	1/22			10.00 [1.40, 71.62]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**

Total events: 10 (Vancomycin), 1 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Placebo Vancomycin

Nelson, Cochrane 2011

Terapia
Metronidazolo vs vancomicina

- Fallimenti
  - Metronidazolo: 22,4%
  - Vancomicina: 14,2%
- Recidive
  - Metronidazolo: 27,1%
  - Vancomicina: 24,0%
- Metro: meno efficace in America

Vardakas, Int J Antimicrob Ag 2012

Cochrane Library
Cochrane Database of Systematic Reviews

Vancomicina vs metronidazolo

Antibiotic treatment for Clostridium difficile associated diarrhea in adults (Review)

Nelson RL, Kelsey P, Leeman H, Meardon N, Patel H, Paul K, Rees R, Taylor B, Wood E, Malakun R

Analysis 2.3. Comparison 2 Metronidazole versus Vancomycin, Outcome 3 Bacteriologic Cure.

Review: Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults

Comparison: 2 Metronidazole versus Vancomycin

Outcome: 3 Bacteriologic Cure

Study or subgroup	Metronidazole n/N	Vancomycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Teasley 1983	21/45	32/56		67.1 %	0.82 [0.56, 1.20]
Wenisch 1996	13/31	14/31		32.9 %	0.93 [0.53, 1.64]
Total (95% CI)	**76**	**87**		**100.0 %**	**0.85 [0.62, 1.17]**

Total events: 34 (Metronidazole), 46 (Vancomycin)

Heterogeneity: $Chi^2 = 0.13$, df = 1 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable

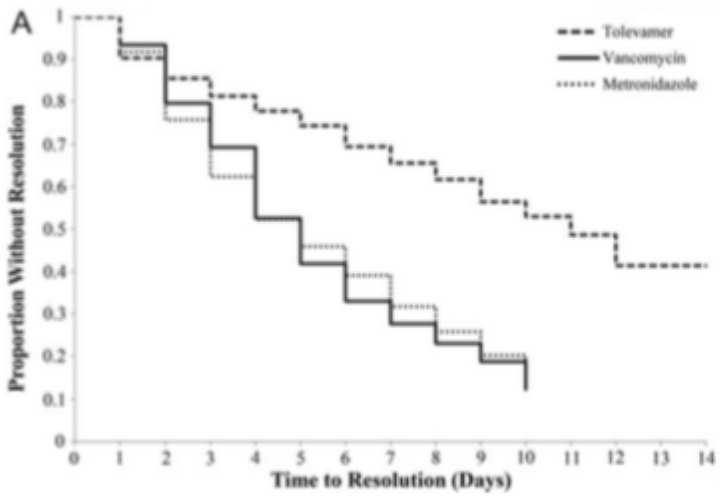
Nelson, Cochrane 2011

MAJOR ARTICLE

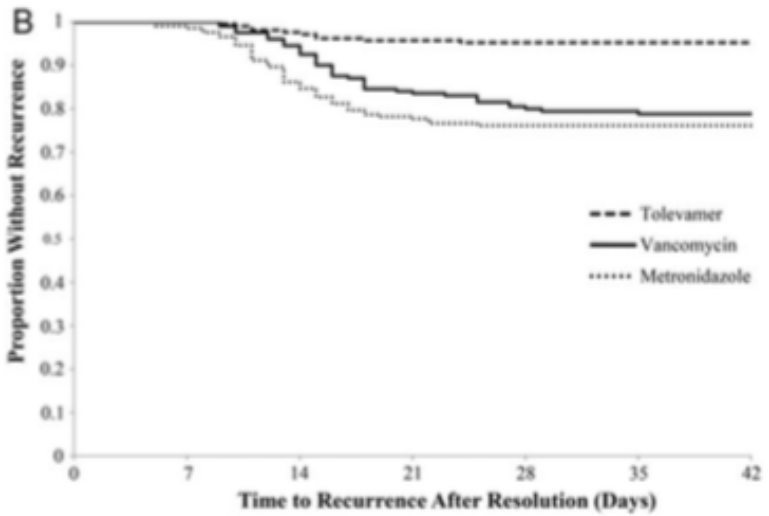
Vancomycin, Metronidazole, or Tolevamer for *Clostridium difficile* Infection: Results From Two Multinational, Randomized, Controlled Trials

Stuart Johnson,[1] Thomas J. Louie,[2] Dale N. Gerding,[1] Oliver A. Cornely,[3] Scott Chasan-Taber,[4,a] David Fitts,[5] Steven P. Gelone,[5] Colin Broom,[5] and David M. Davidson[4,b]; for the Polymer Alternative for CDI Treatment (PACT) investigators

Guarigione



Recidiva



Johnson, Clin Infect Dis 2014

Terapia

Forma	Terapia	Durata (gg)
Lieve o moderata	Metronidazolo 500 mg ogni 8 ore per os	10 – 14
	Metronidazolo 500 mg ogni 8 ore ev (+ vancomicina 125 mg ogni 6 ore per os?)	10 – 14
Grave	Vancomicina 125 mg ogni 6 ore per os	10 – 14
	Vancomicina 500 mg ogni 6 ore per os	10 – 14
Complicata	Vancomicina 500 mg ogni 6 ore per os + vancomicina rettale 250 mg ogni 12 ore + metronidazolo 500 mg ogni 8 ore ev	??

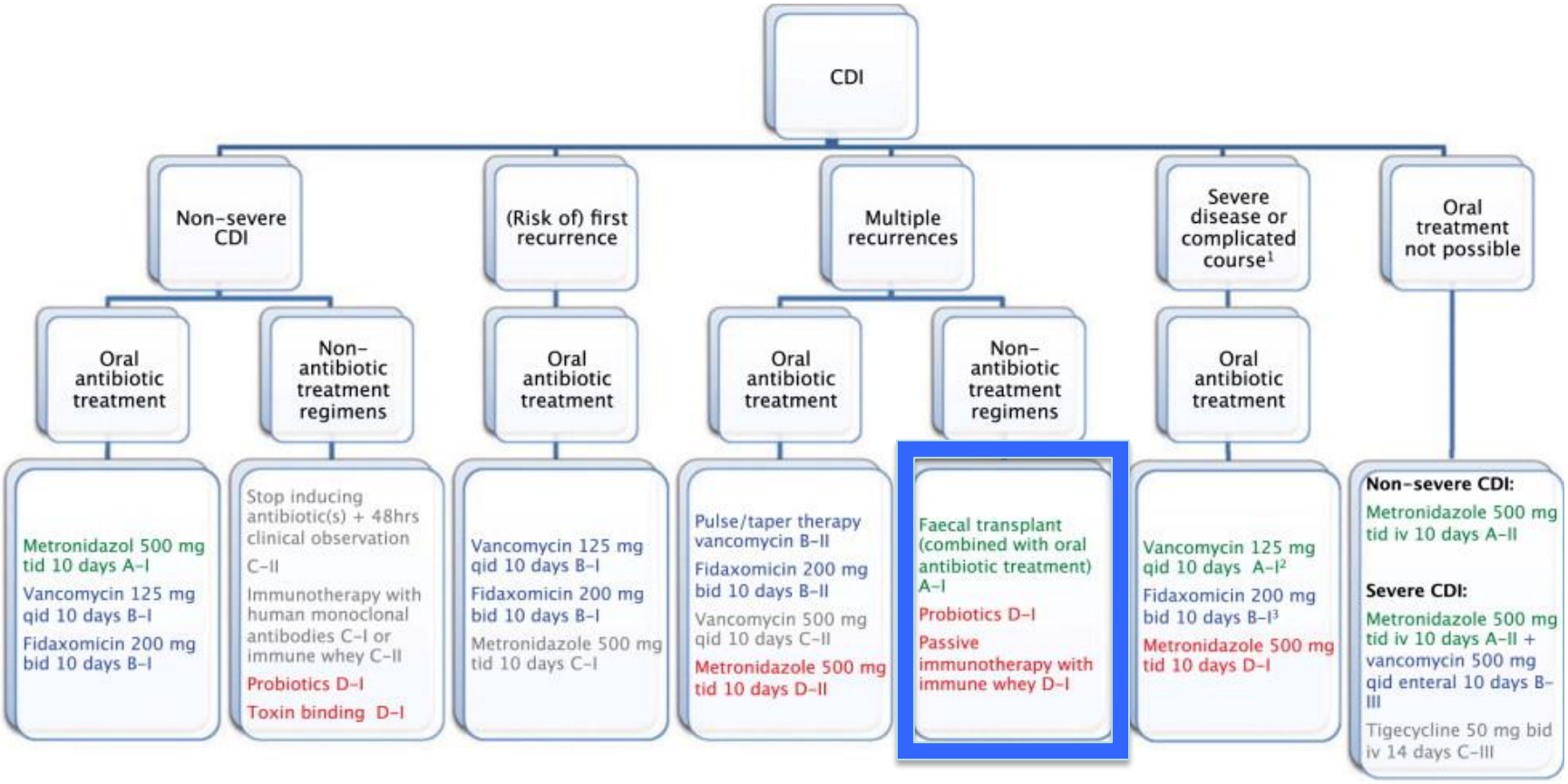
Bagdasarian, JAMA 2015

Terapia - recidive

Recidiva	Terapia	Durata (gg)
Prima	Metronidazolo 500 mg ogni 8 ore per os o Vancomicina 125 mg ogni 6 ore per os	A scalare
Seconda o più	Vancomicina 500 mg ogni 6 ore per os	??
	Fidaxomicina 200 mg ogni 12 ore per os	??

Bagdasarian, JAMA 2015

Terapia – ESCMID 2014



Debast, CMI 2014

Terapia – SHEA/IDSA 2010

Clinical definition	Supportive clinical data	Recommended treatment	Strength of recommendation
Initial episode, mild or moderate	Leukocytosis with a white blood cell count of 15,000 cells/μL or lower and a serum creatinine level less than 1.5 times the premorbid level	Metronidazole, 500 mg 3 times per day by mouth for 10–14 days	A-I
Initial episode, severe[a]	Leukocytosis with a white blood cell count of 15,000 cells/μL or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level	Vancomycin, 125 mg 4 times per day by mouth for 10–14 days	B-I
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin	C-III
First recurrence	…	Same as for initial episode	A-II
Second recurrence	…	Vancomycin in a tapered and/or pulsed regimen	B-III

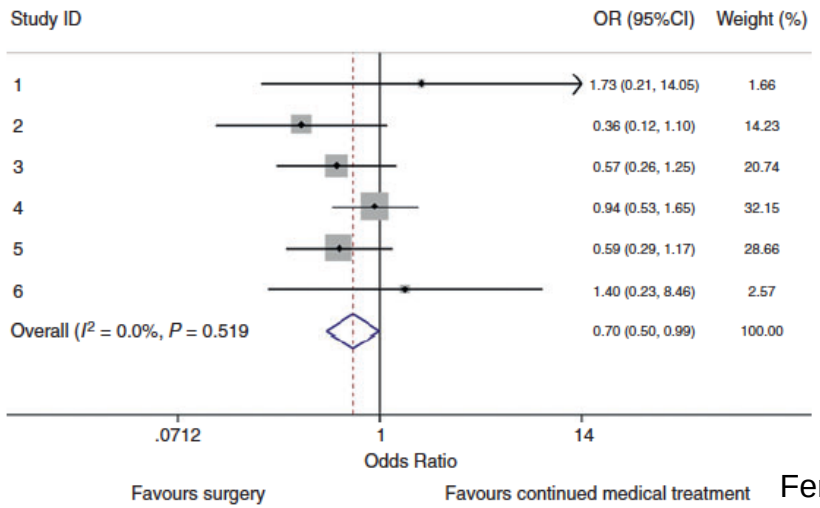
Cohen, ICHE 2010

E la chirurgia?

La colectomia totale non aumenta la mortalità

Indicazione: Colite fulminante - almeno 1 di:

- Ricovero in UTI
- Valutazione per chirurgia
- Morte per colite da *C. difficile*



Ferrada , J Trauma Acute Care Surg 2014; Stewart, Colorect Dis 2013

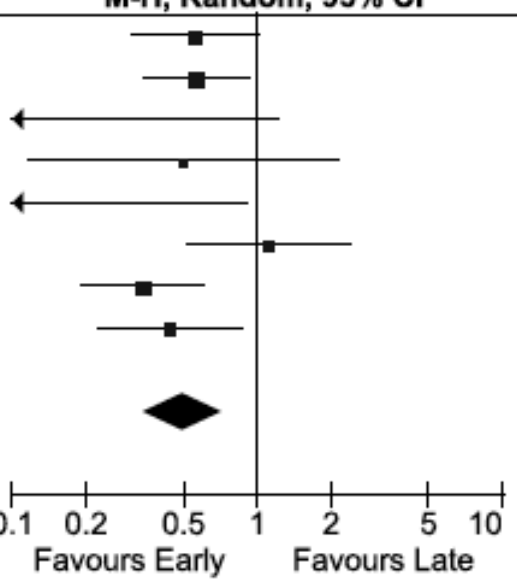
Quando la chirurgia?

- Precoce meglio che tardiva
- Prima di shock o necessità di amine o insufficienza d'organo

	Early surgery		Late surgery			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Ali	11	27	8	11	18.9%	0.56 [0.31, 1.00]	
Hall	11	23	11	13	22.1%	0.57 [0.35, 0.92]	
Hermsen	0	9	6	9	1.7%	0.08 [0.00, 1.19]	
Koss	2	8	3	6	5.4%	0.50 [0.12, 2.12]	
Markelov	0	8	5	5	1.7%	0.06 [0.00, 0.91]	
Perera	10	21	6	14	14.2%	1.11 [0.52, 2.36]	
Sailhamer	13	57	14	21	19.4%	0.34 [0.19, 0.60]	
Seder	8	32	21	37	16.5%	0.44 [0.23, 0.85]	
Total (95% CI)		**185**		**116**	**100.0%**	**0.50 [0.35, 0.72]**	
Total events	55		74				

Heterogeneity: Tau² = 0.09; Chi² = 11.42, df = 7 (P = 0.12); I² = 39%

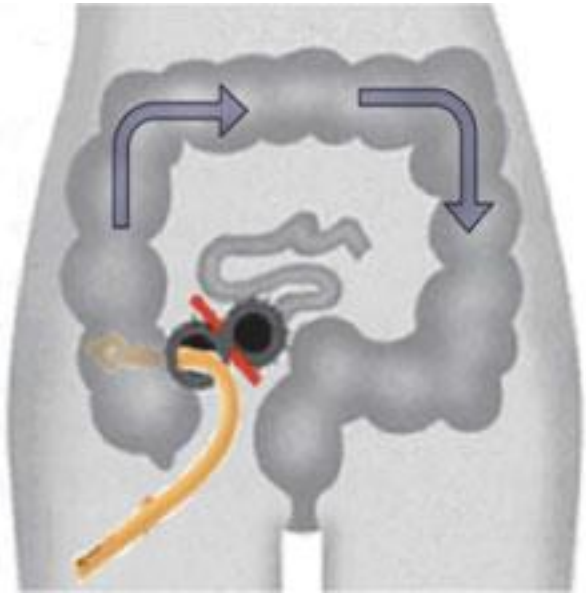
Test for overall effect: Z = 3.73 (P = 0.0002)



Ferrada , J Trauma Acute Care Surg 2014

Quale intervento

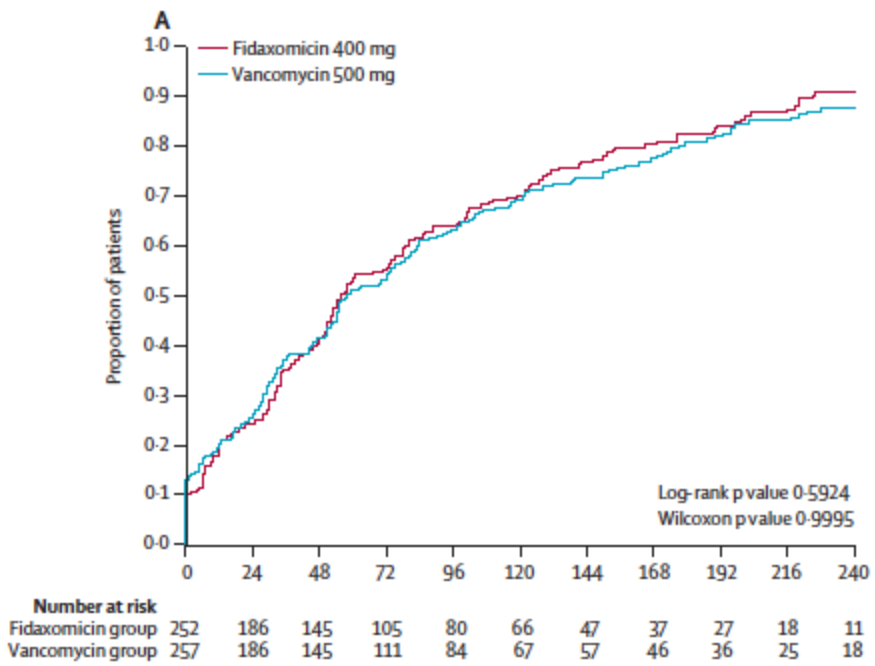
- Colectomia o subcolectomia
- Ileostomia con lavaggio colico
  - Mortalità ridotta (19% vs 50%, p=0,006)
  - Conservazione del colon in 39/42 paziesnti

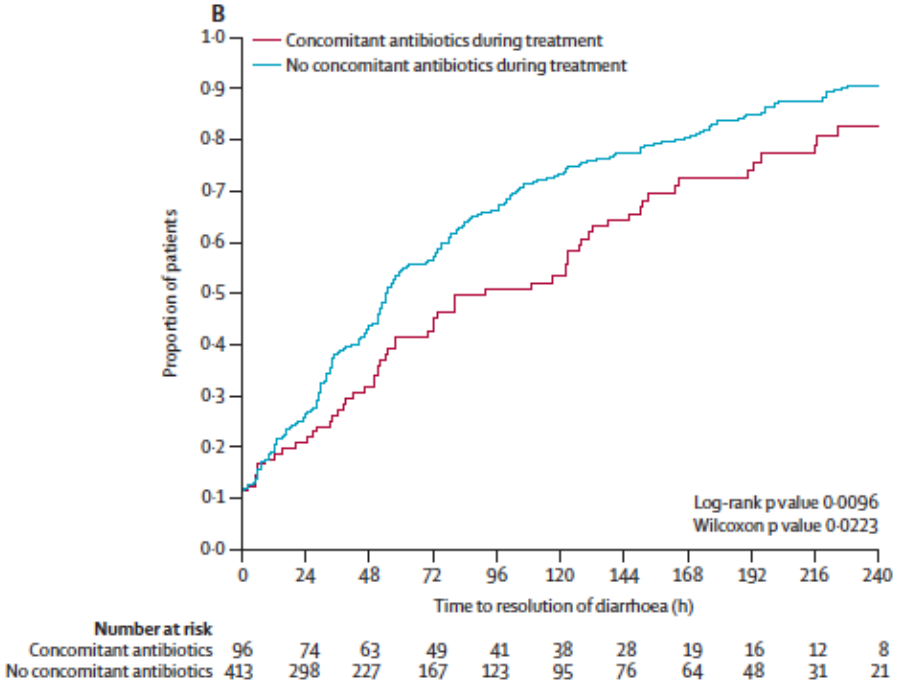


1. Creation of diverting loop ileostomy.
2. Intraoperative antegrade colonic lavage with 8 liters of warmed PEG3350/electrolyte solution via ileostomy.
3. Postoperative antegrade colonic enemas with vancomycin (500 mg in 500 mL X 10 days) via ileostomy.

Fidaxomicina

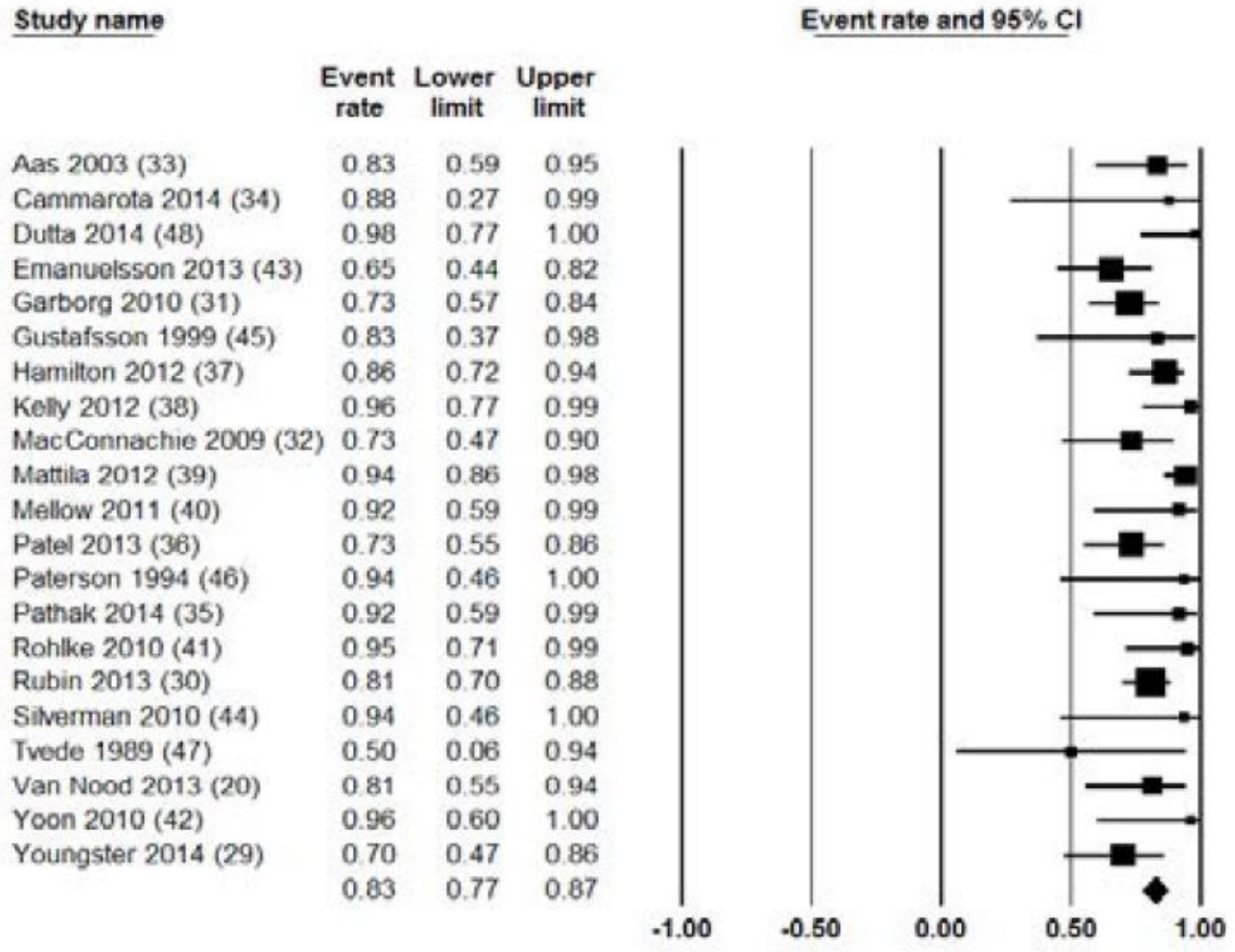
- Totale pazienti
- Pazienti in antibiotico





Cornely, LID 2012

Trapianto di microbiota fecale



Drekonja D, VA ESP Project #09-009; 2014.

Trapianto di microbiota fecale congelato vs fresco

- 219 pazienti: 108 congelato, 111 fresco
- Successo:
  - Congelato: 83.5%
  - Fresco: 85.1%
  - differenza, −1.6% [95% CI, –10.5% to ∞]; P = .01 per non-inferiorità).
  - mITT: P < .001 for non-inferiorità.
  - Eventi avversi: equivalenti

Lee C, JAMA; 2016.

Altre terapie

- Tigeciclina: studi in corso
- Surotomicina: studi in corso
- Cadazolid: studi in corso

- Colestipol e colestiramina: non efficaci
- Tolevamer: inferiore

- Siero anti-tossina A: può proteggere
- Vaccino: studi in corso
- Pool di immunoglobuline: potenzialmente attivo
- Ab monoclonali neutralizzanti: meno recidive

Cochrane Library
Cochrane Database of Systematic Reviews

Teicoplanina vs vancomicina

Antibiotic treatment for Clostridium difficile associated diarrhea in adults (Review)

Nelson RL, Kelsey P, Leeman H, Meardon N, Patel H, Paul K, Rees R, Taylor B, Wood E, Malakun R

Analysis 4.2. Comparison 4 Teicoplanin versus Vancomycin, Outcome 2 Symptomatic Cure.

Review: Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults

Comparison: 4 Teicoplanin versus Vancomycin

Outcome: 2 Symptomatic Cure

Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
de Lalla 1992	23/27	16/24		42.7 %	1.28 [0.92, 1.77]
Wenisch 1996	25/28	24/31		57.3 %	1.15 [0.92, 1.45]
Total (95% CI)	**55**	**55**		**100.0 %**	**1.21 [1.00, 1.46]**

Total events: 48 (Teicoplanin), 40 (Vancomycin)
Heterogeneity: $Chi^2 = 0.27$, $df = 1$ ($P = 0.60$); $I^2 = 0.0\%$
Test for overall effect: $Z = 1.92$ ($P = 0.055$)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Vancomycin Teicoplanin

Analysis 4.4. Comparison 4 Teicoplanin versus Vancomycin, Outcome 4 Bacteriologic Cure.

Review: Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults

Comparison: 4 Teicoplanin versus Vancomycin

Outcome: 4 Bacteriologic Cure

Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wenisch 1996	23/28	14/31		100.0 %	1.82 [1.19, 2.78]
Total (95% CI)	**28**	**31**		**100.0 %**	**1.82 [1.19, 2.78]**

Total events: 23 (Teicoplanin), 14 (Vancomycin)
Heterogeneity: not applicable
Test for overall effect: $Z = 2.76$ ($P = 0.0058$)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Vancomycin Teicoplanin

Nelson, Cochrane 2011

- Introduzione
- Terapia
- **Prevenzione**
- Un’esperienza personale
- Conclusioni

Prevenzione

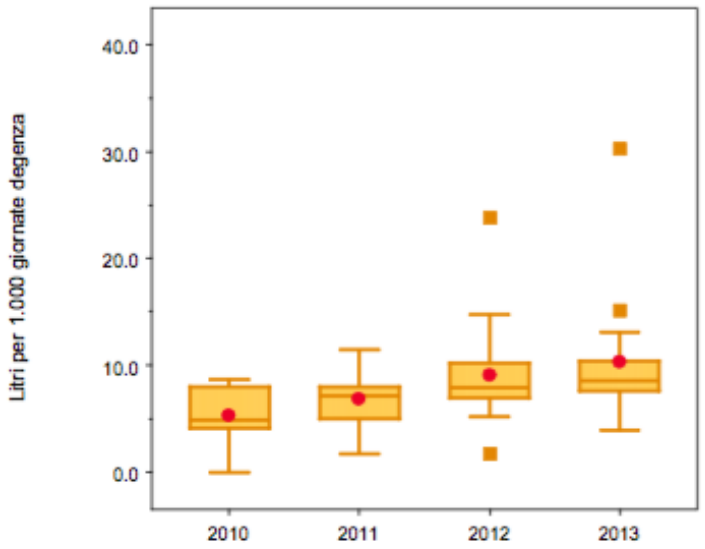
Farmaci

Mani

Selezione

Trasmissione

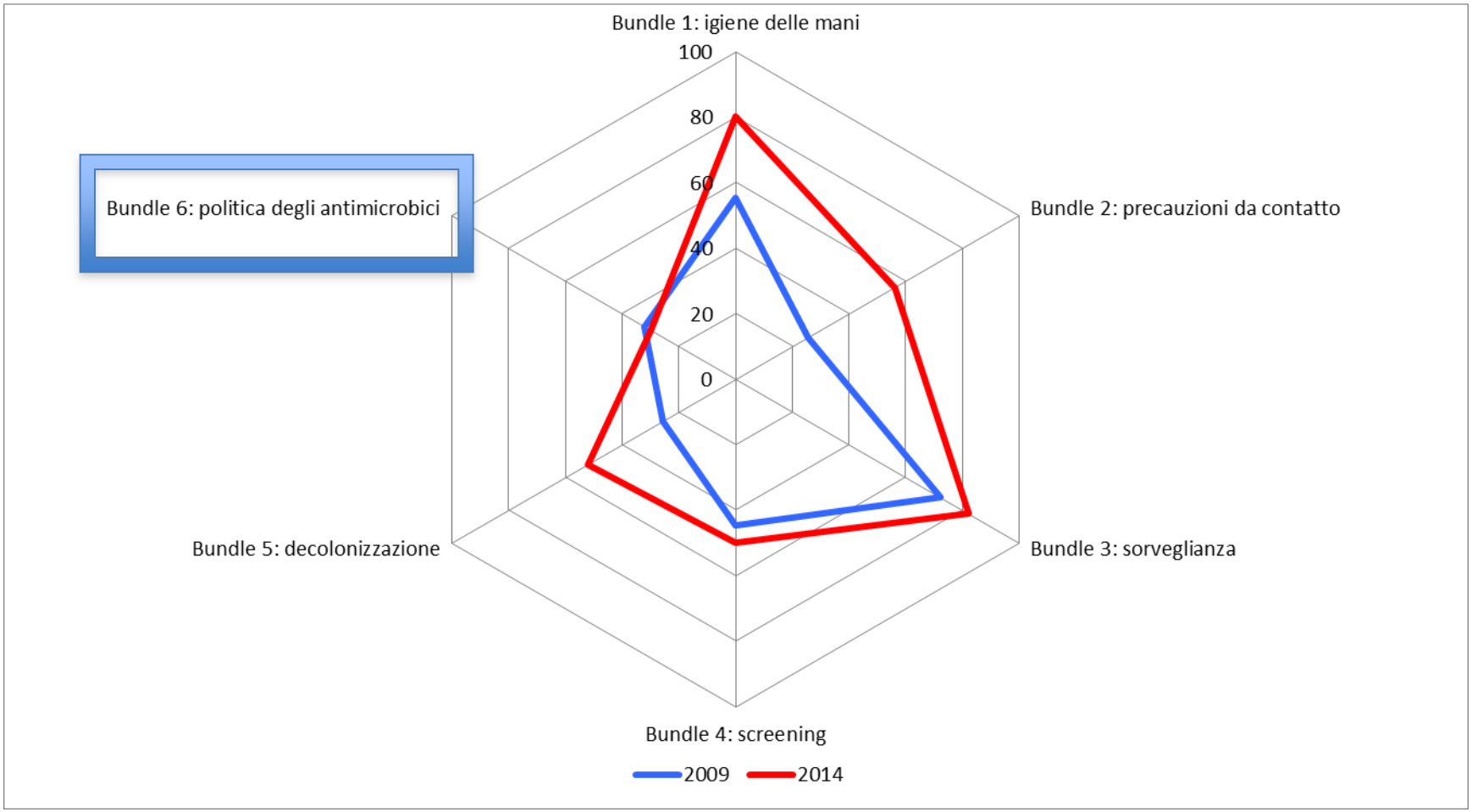
Consumo di soluzione idroalcolica - RER



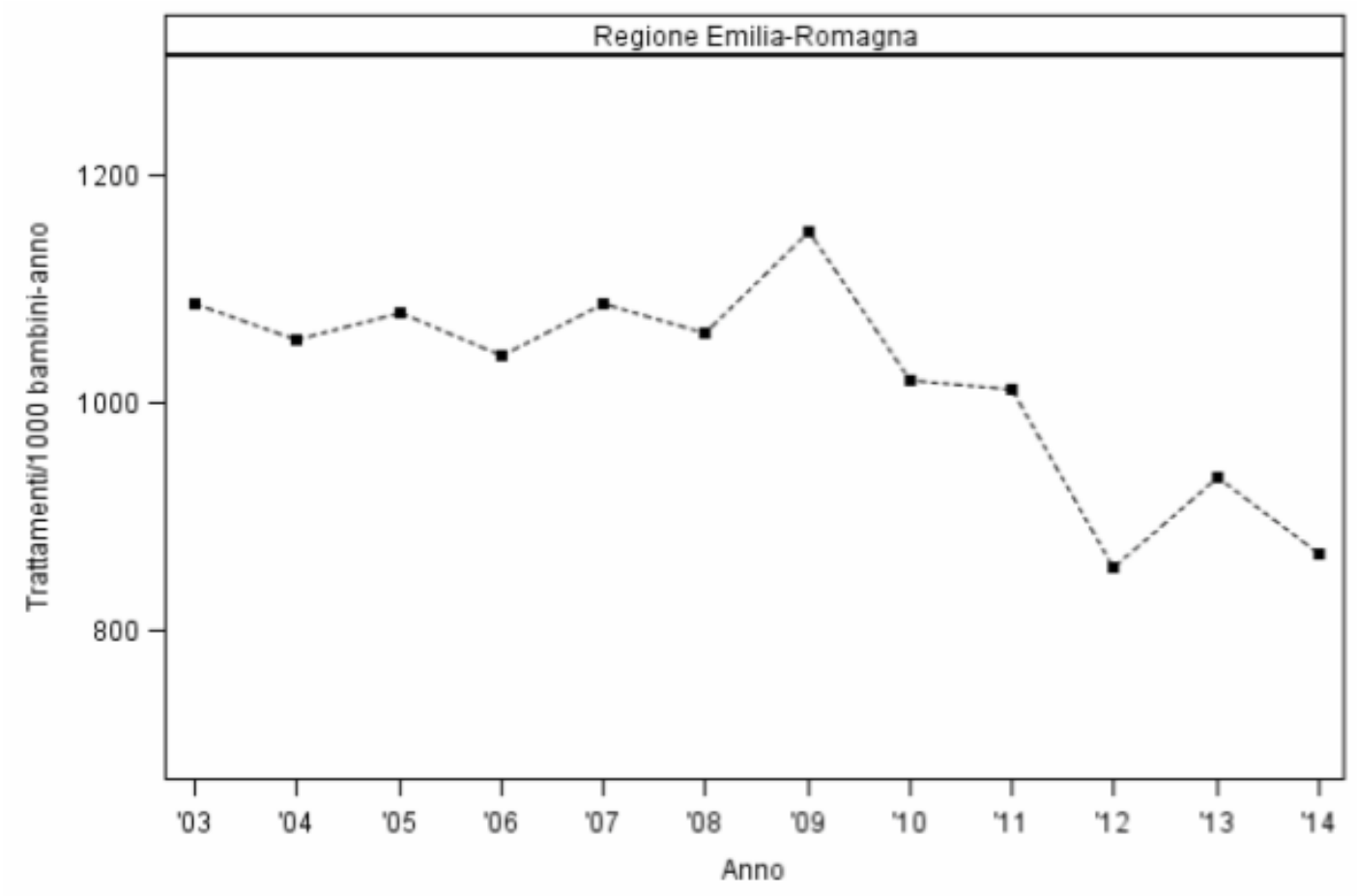
Parenti, ASSR RER 2015

Progetto ProSA-2

50 ospedali, 16% dei ricoveri in Italia

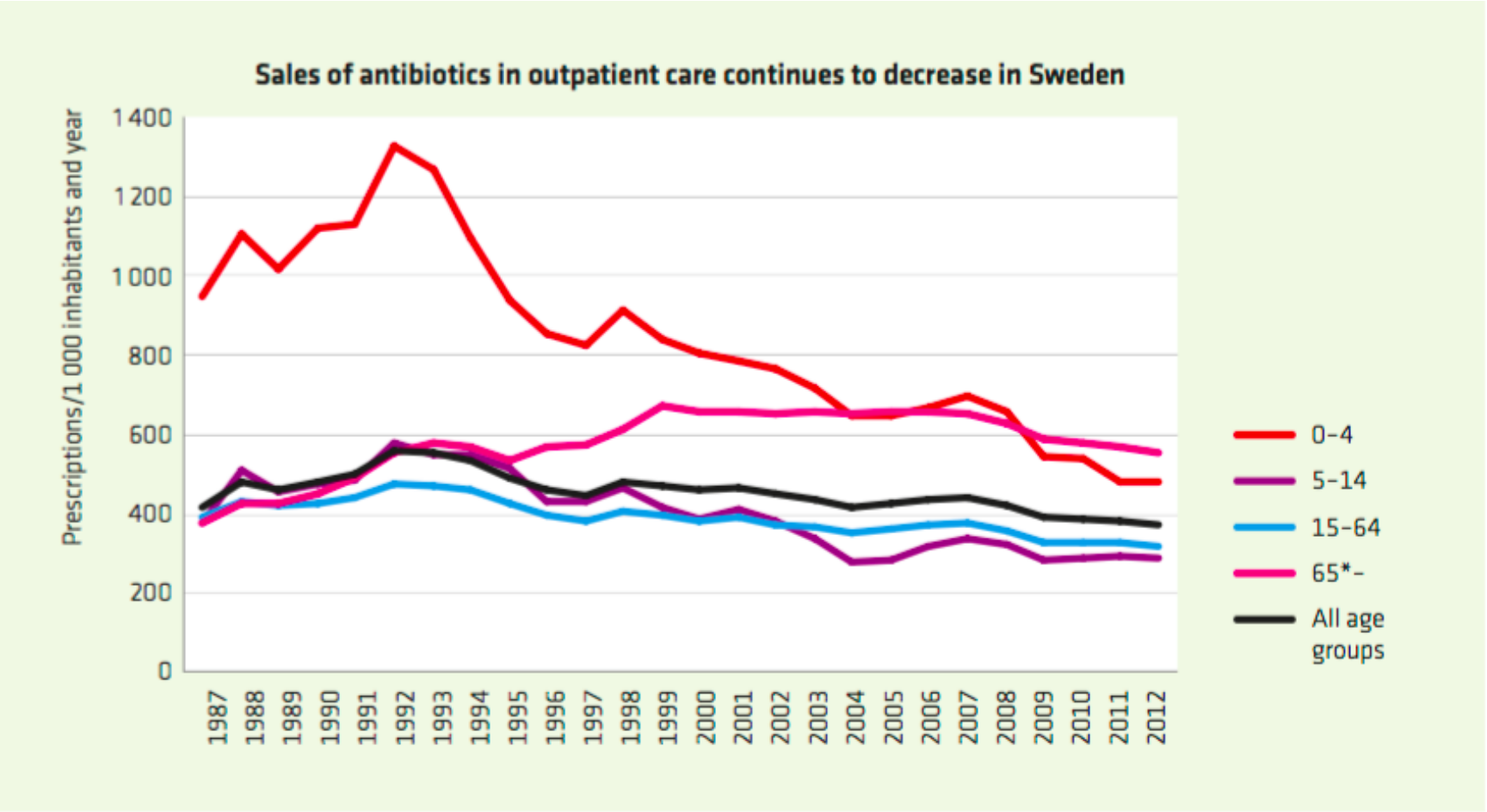


Tasso di trattamento per anno



Gagliotti, ASSR RER 2015

Prescrizione in Svezia 1987 - 2012

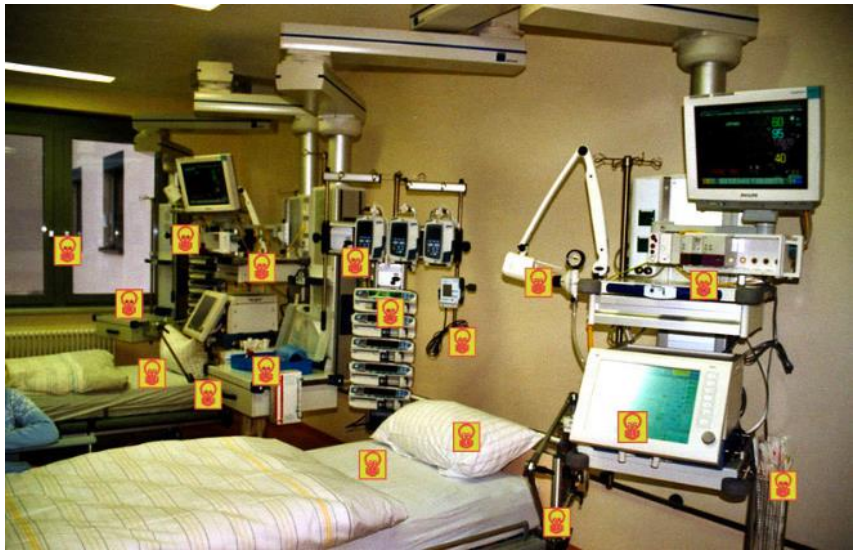


Isolamento

- Stanza singola
- Lavaggio delle mani con **acqua e sapone**
- Guanti
- Sovracamice
- Materiale dedicato

Contaminazione ambientale

- Comodini
- Letti
- Bagni & zone smaltimento deiezioni
- Pavimenti
- Tappeti



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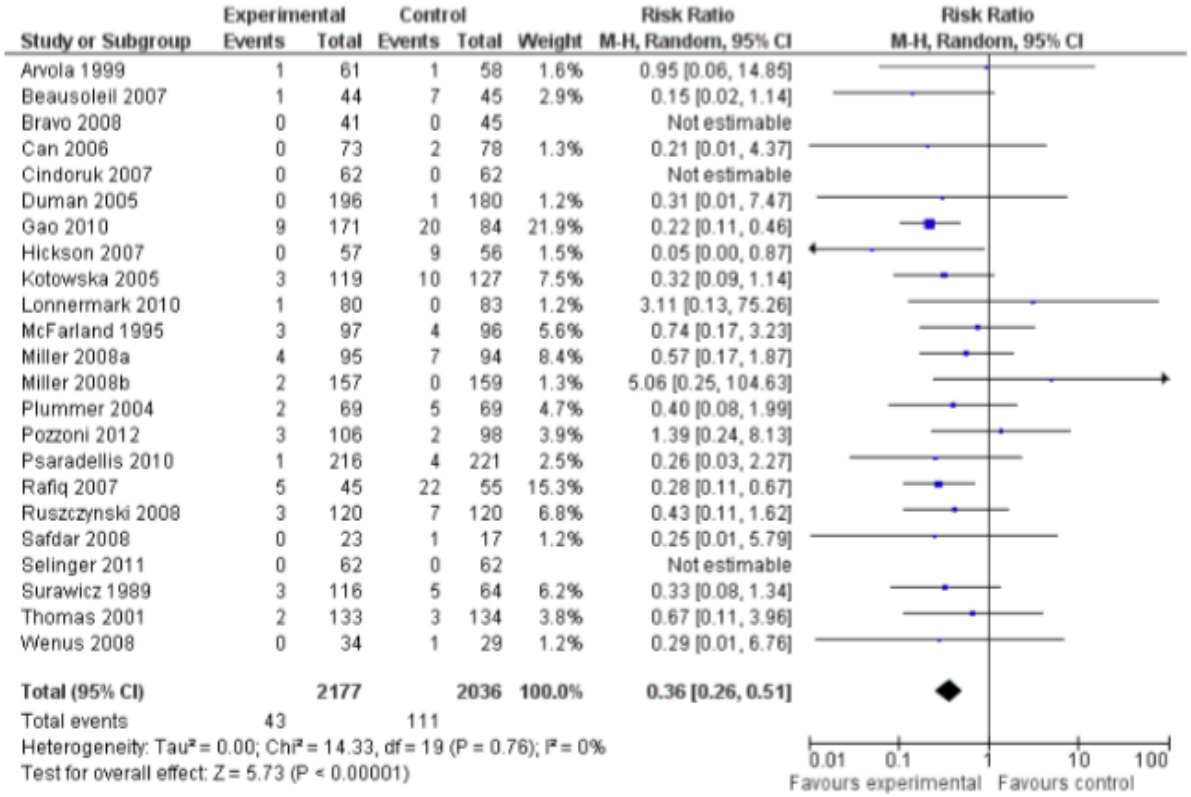
Cochrane Database of Systematic Reviews

Probiotici

Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children (Review)

Goldenberg JZ, Ma SSY, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC

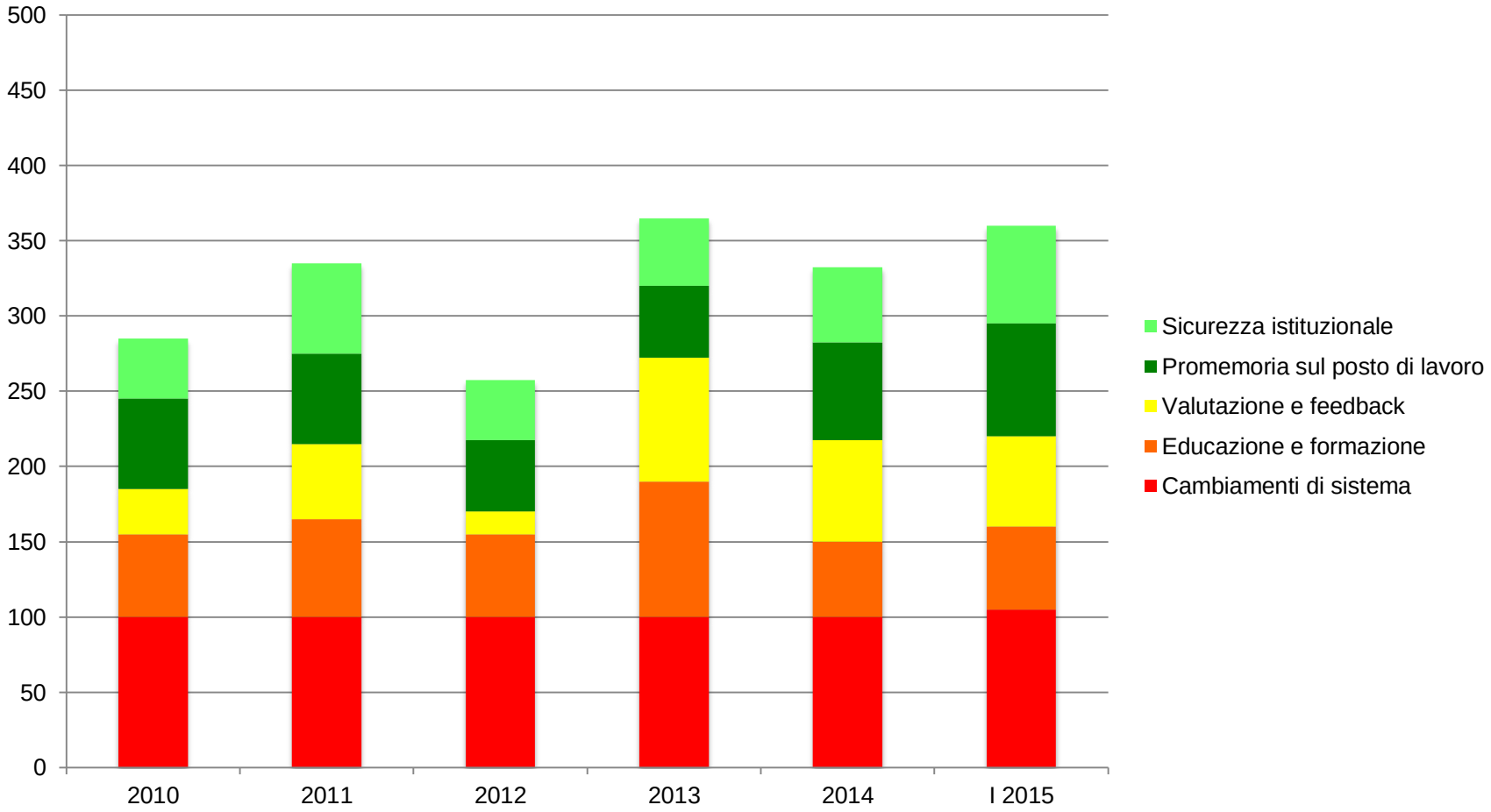
Figure 3. Forest plot of comparison: 1 C. difficile associated diarrhea, outcome: 1.1 Incidence CDAD: complete case.



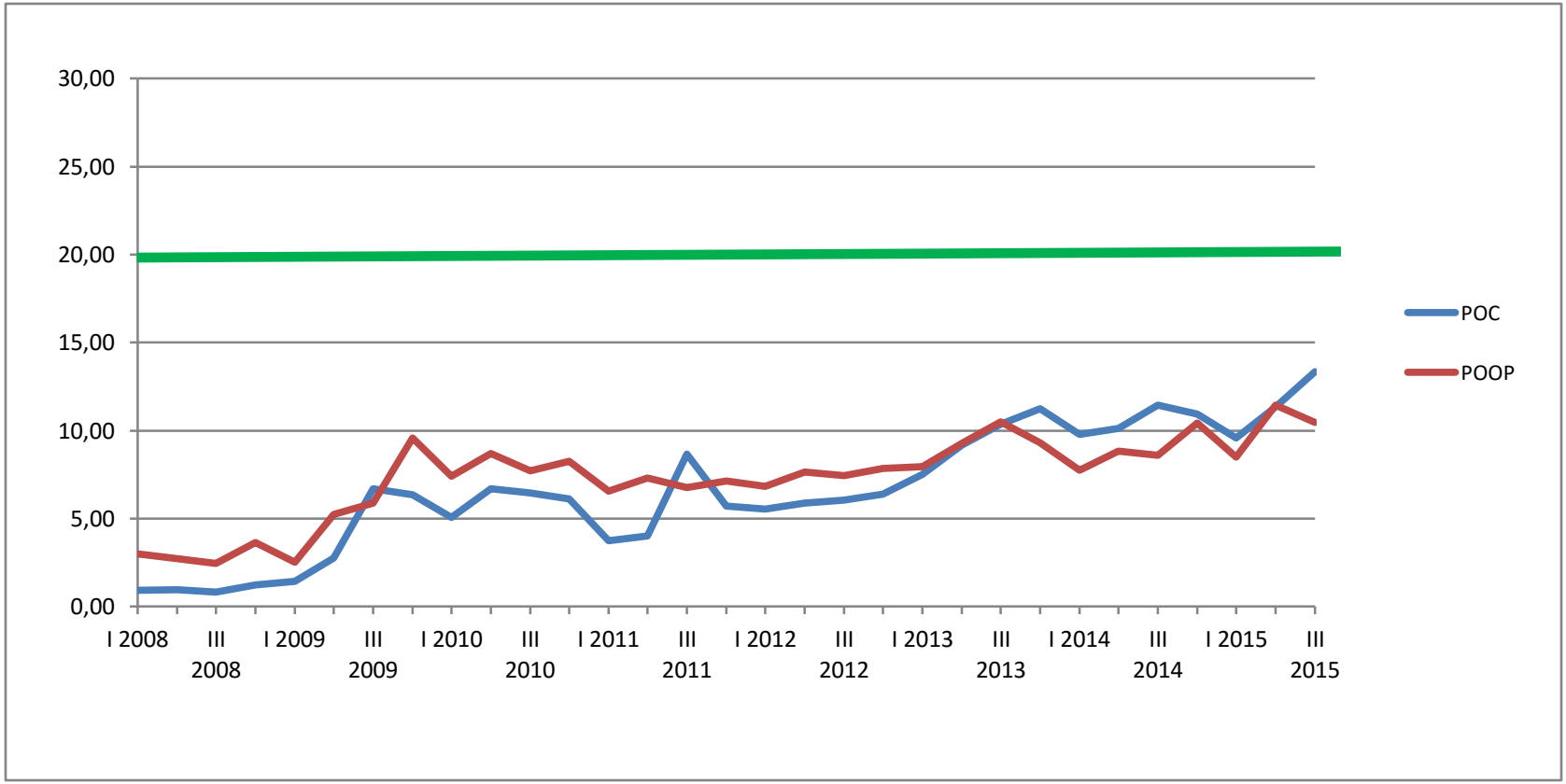
Goldenberg, Cochrane 2013

- Introduzione
- Terapia
- Prevenzione
- **Un’esperienza personale**
- Conclusioni

Framework di autovalutazione

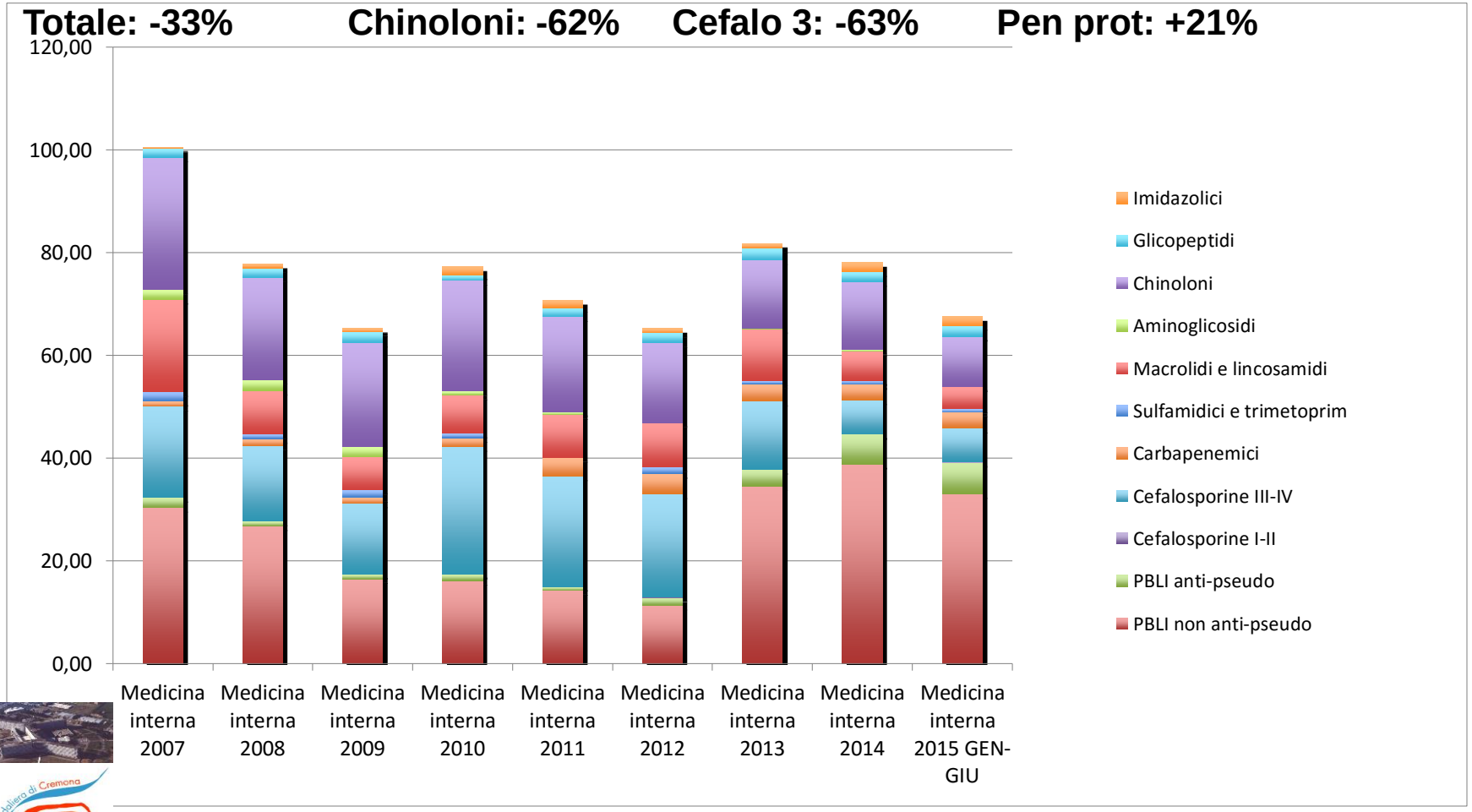


Consumo di soluzioni idroalcoliche POC & POOP 2008-2015



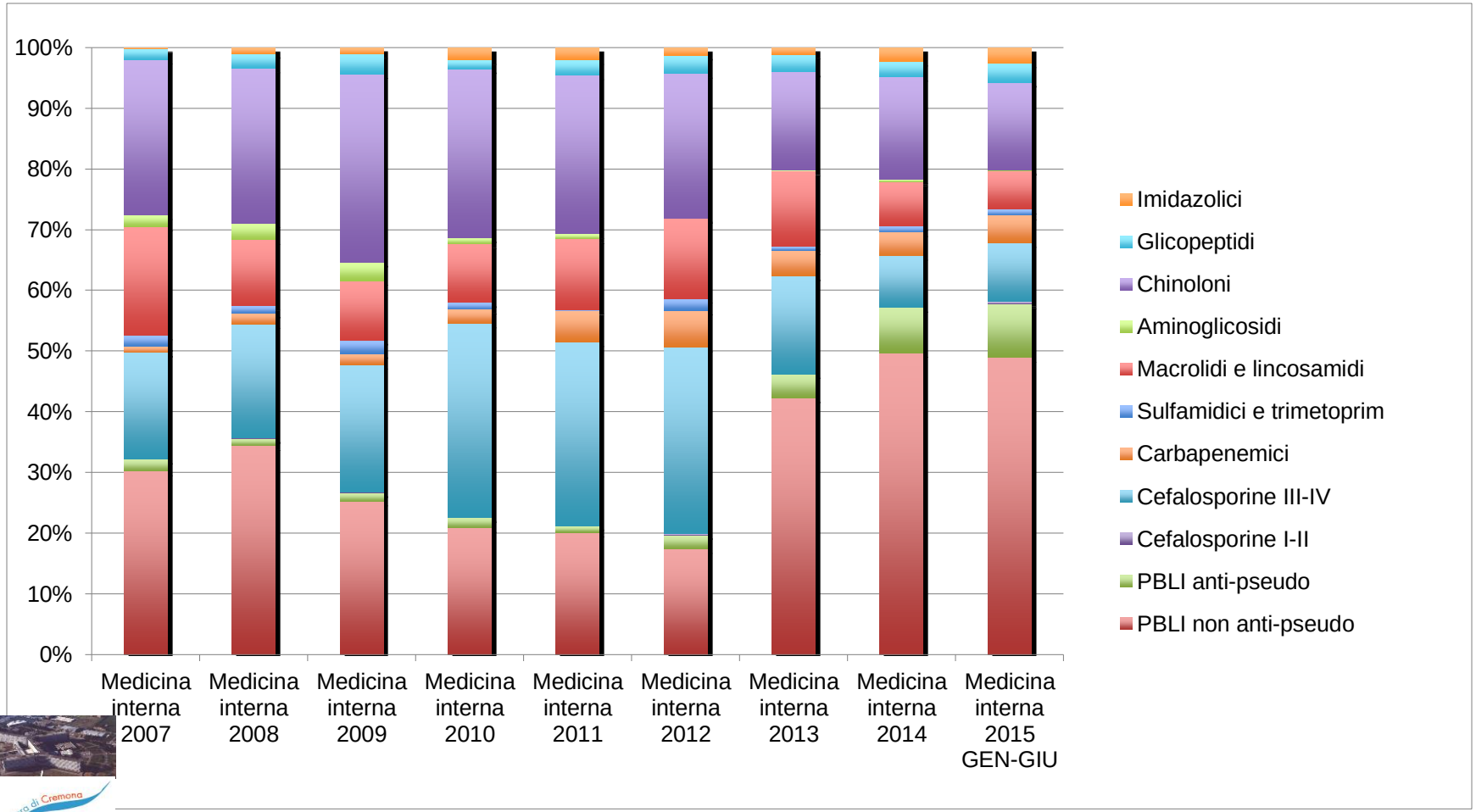
Consumo di antibiotici in medicina

DDD/100 giorni paziente
2007 – 2015

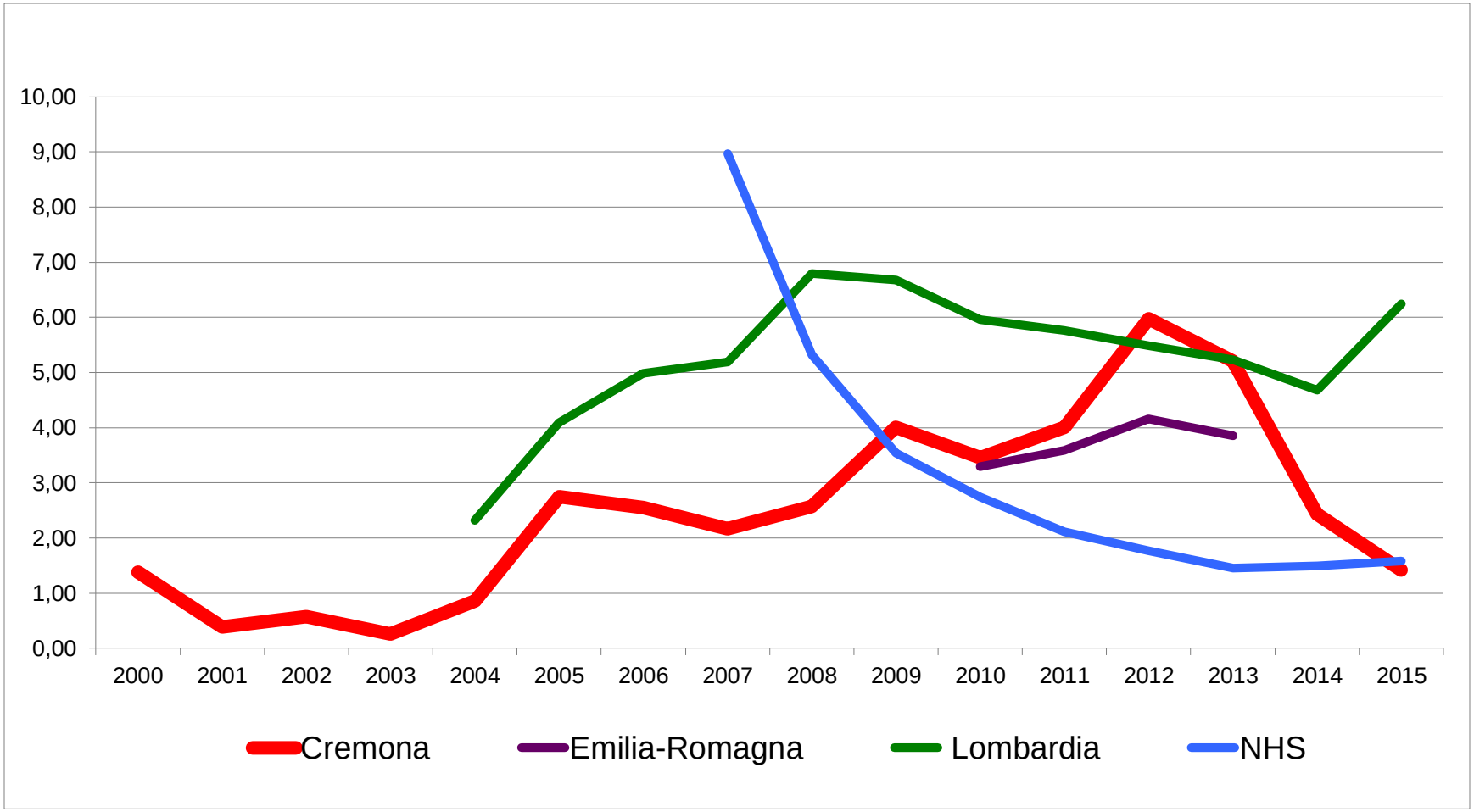


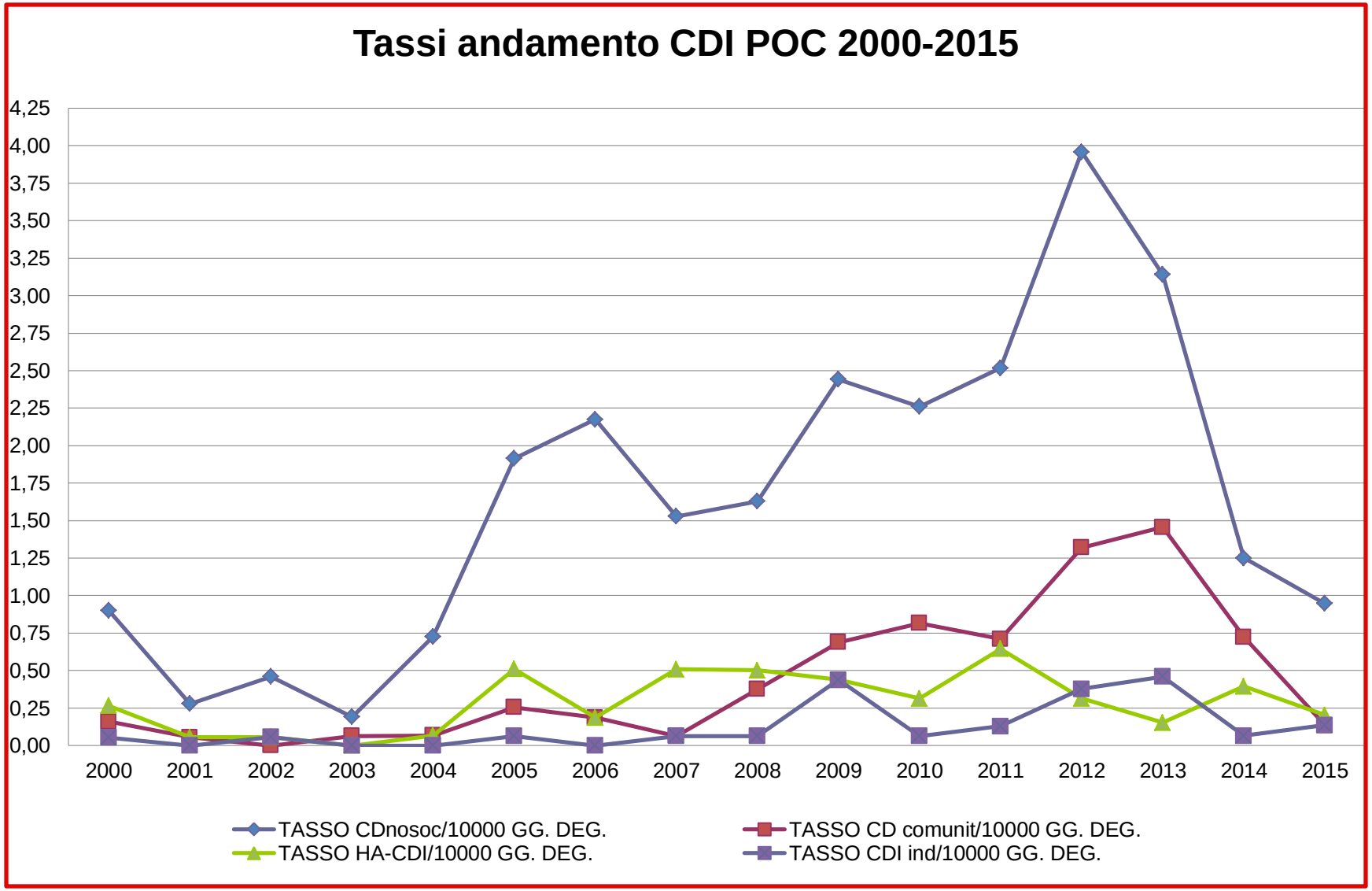
Consumo di antibiotici in medicina

proporzioni delle prescrizioni per classe
2007 – 2015



Tasso di CDI per 10.000 giornate di degenza




Tassi andamento CDI POC 2000-2015
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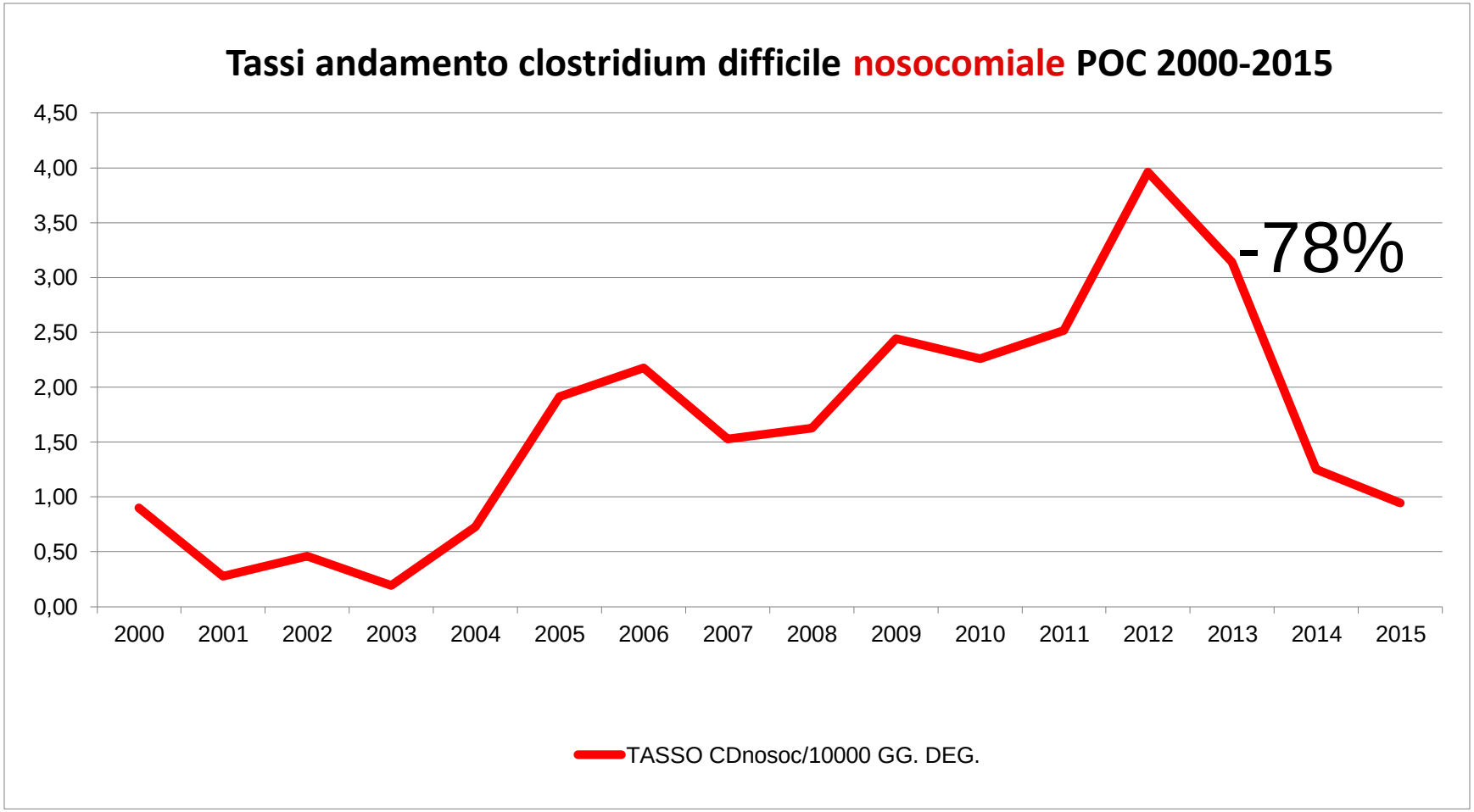
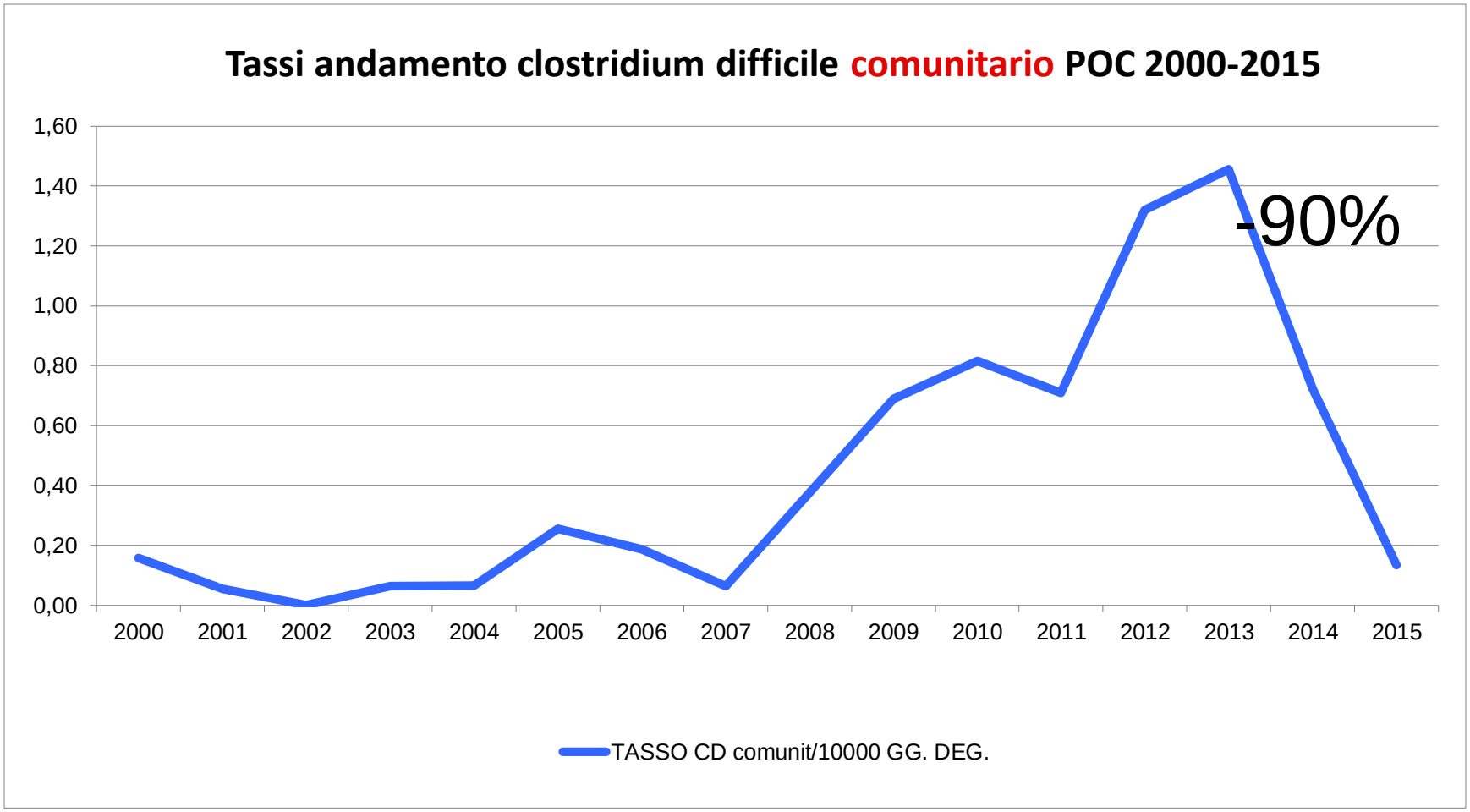
TASSO CDnosoc/10000 GG. DEG.
TASSO CD comunit/10000 GG. DEG.
TASSO HA-CDI/10000 GG. DEG.
TASSO CDI ind/10000 GG. DEG.


Tassi andamento clostridium difficile nosocomiale POC 2000-2015
4,50
4,00
3,50
3,00
2,50
2,00
1,50
1,00
0,50
0,00
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
-78%
TASSO CDnosoc/10000 GG. DEG.


Tassi andamento clostridium difficile comunitario POC 2000-2015
1,60
1,40
1,20
1,00
0,80
0,60
0,40
0,20
0,00
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
-90%
TASSO CD comunit/10000 GG. DEG.

- Introduzione
- Terapia
- Prevenzione
- Un’esperienza personale
- **Conclusioni**

Piero Manzoni, 1961

Terapia basata sulla gravità del paziente

Trapianto di feci: da organizzare

Casi gravi: considerare con attenzione la chirurgia

Mettere in atto programmi di:

- politica degli antibiotici
- controllo delle infezioni
- igiene delle mani

Grazie

Buon appetito!