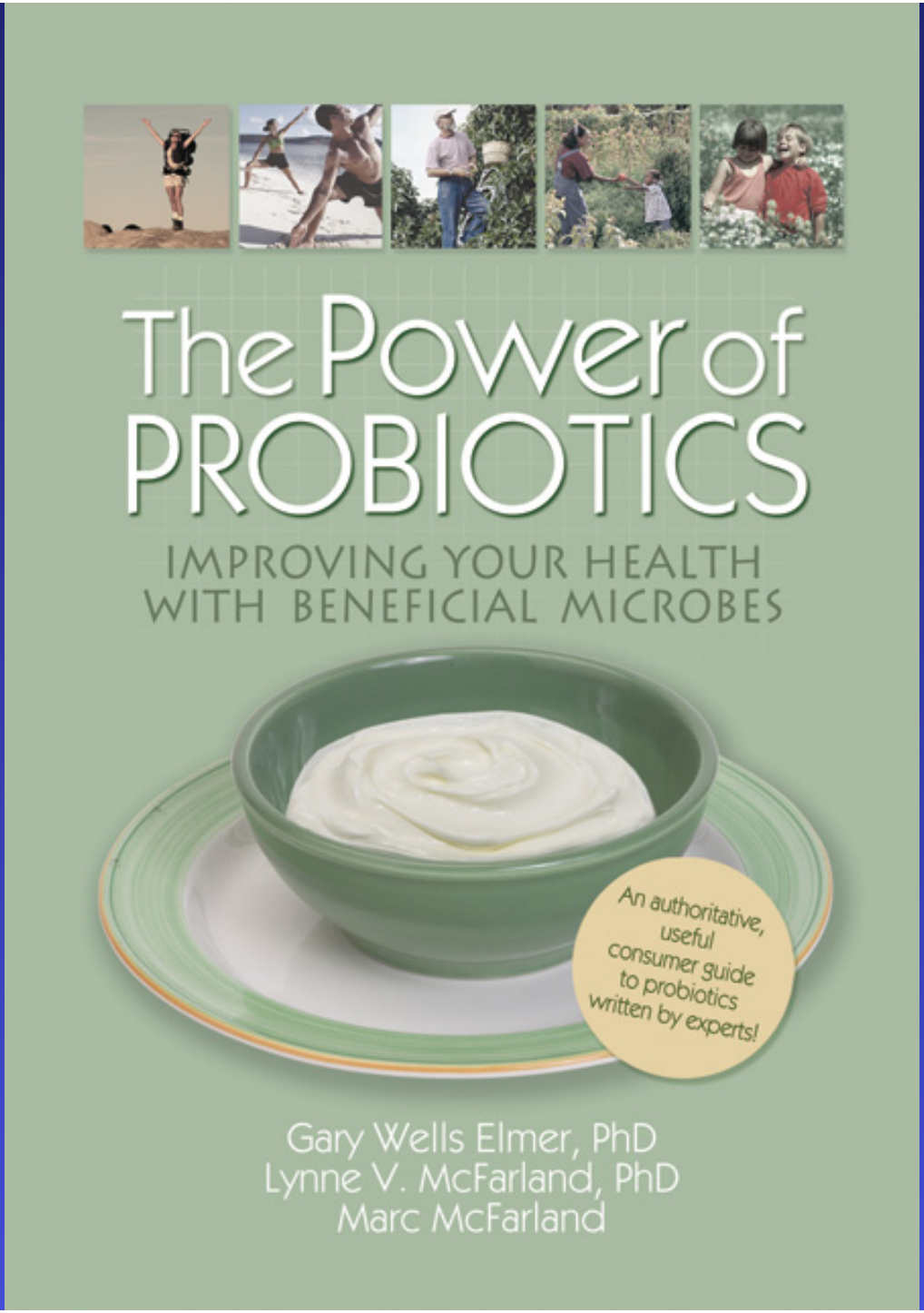


Haworth Press 2007

Probiotics Terms:

- **Probiotic** – Probiotics are live microorganisms (bacteria or yeasts) which, when administered in adequate amounts, confer a health benefit on the host
- **Prebiotic** - nutritional supplement taken to increase the amounts of beneficial bacterial in the gut or vagina. Example "FOS" (fructose oligosaccharides)
- **Synbiotic** – combination of a probiotic and a prebiotic
- **Biotherapeutic agent** - microorganism used for specific therapeutic activity in humans
- **Nutriceutical** - food products with beneficial effects in preventing or treating diseases

Probiotics- basic definition

- Joint Food and Agriculture Organization/World Health Organization Working Group's definition of probiotics: “Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host”

Historical Prospective- then to now

- Yogurts and other fermented dairy products
- General probiotics- Lactobacillus caseii, L. acidophilus, etc
- Specific probiotics selected
- Probiotic yogurts- Activia, Colon health, etc
- Opimization of probiotic therapy

Functions of Normal Flora

- Digestion
- Production of vitamins
- Mucosal maturation
- Stimulate Immune System
- Attachment
- Intestinal transit
- Colonization resistance

The US Market for Probiotics (source: SRI Consulting, Menlo Park, CA)

$764M (2005); ↑ 10%/yr

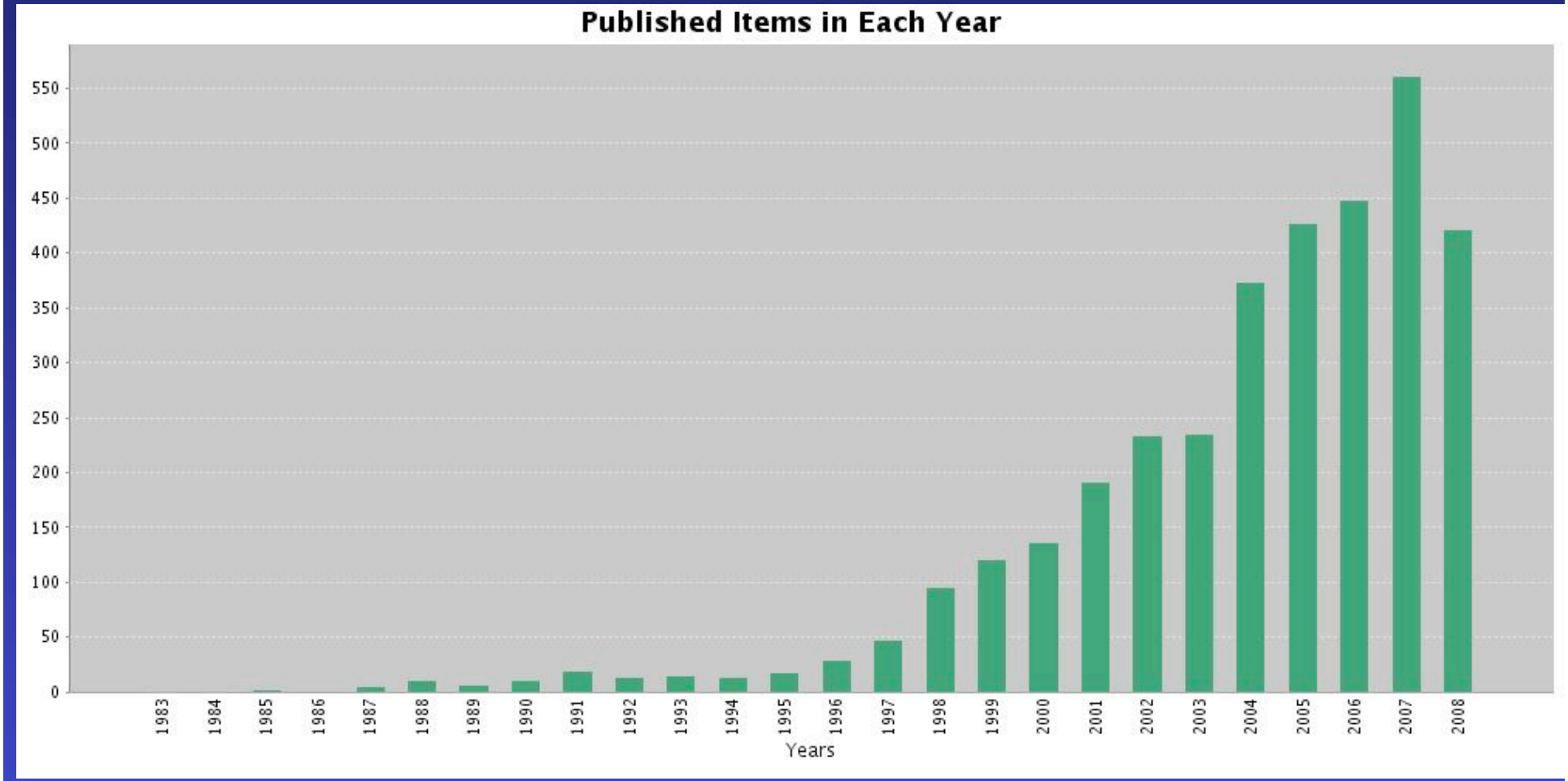
Herbal products $4790 (2007); ↑ 4%/yr

About 2M consumers use probiotics (2006)

- Probiotic foods vs probiotic therapeutics

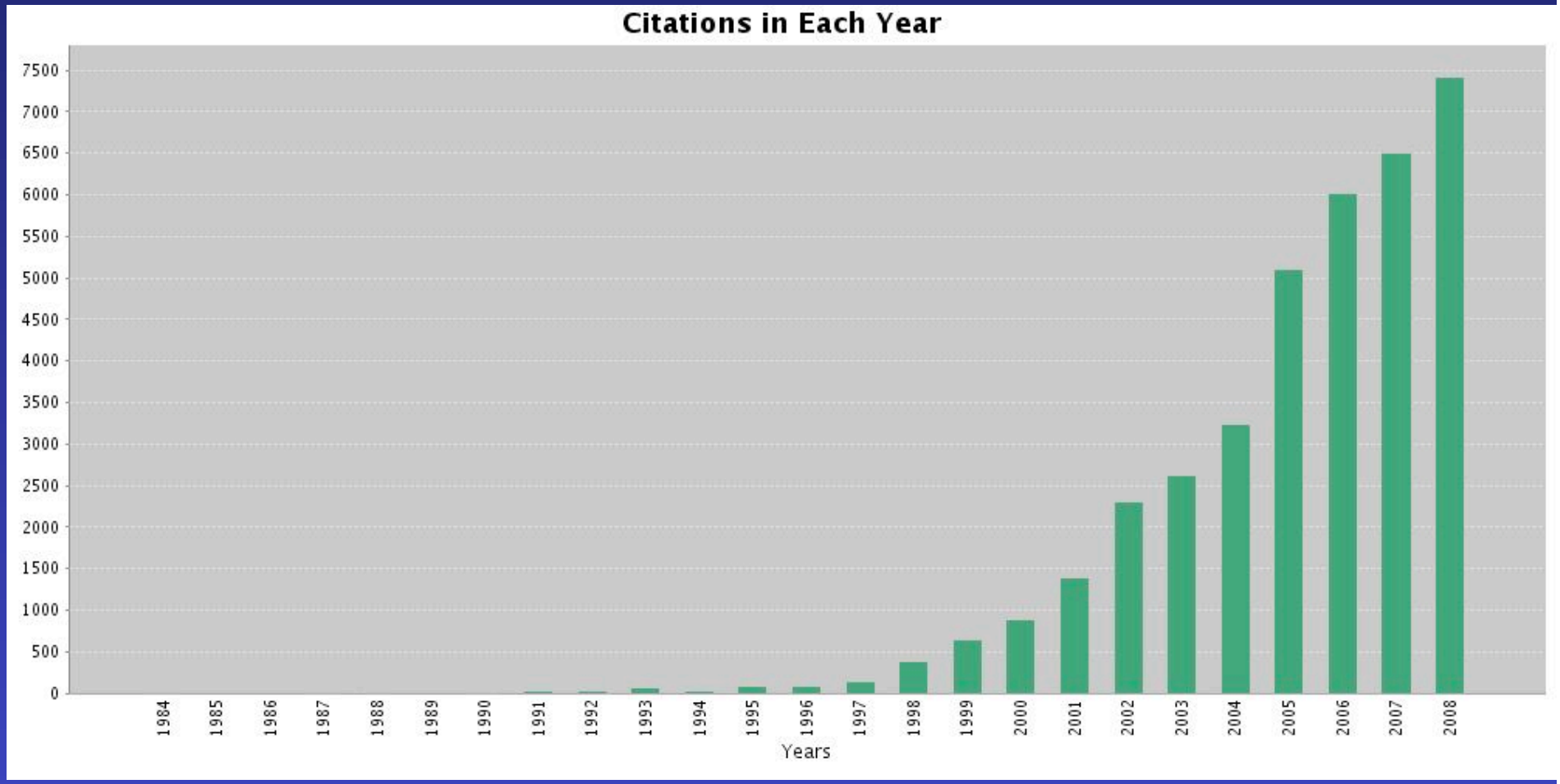
Myths about Probiotics

- Not well studied
- Are narrow spectrum agents for diarrhea only
- Not well regulated (partly true)
- Cultures are all therapeutically similar
- Optimum therapeutic dose is about 1 billion CFU

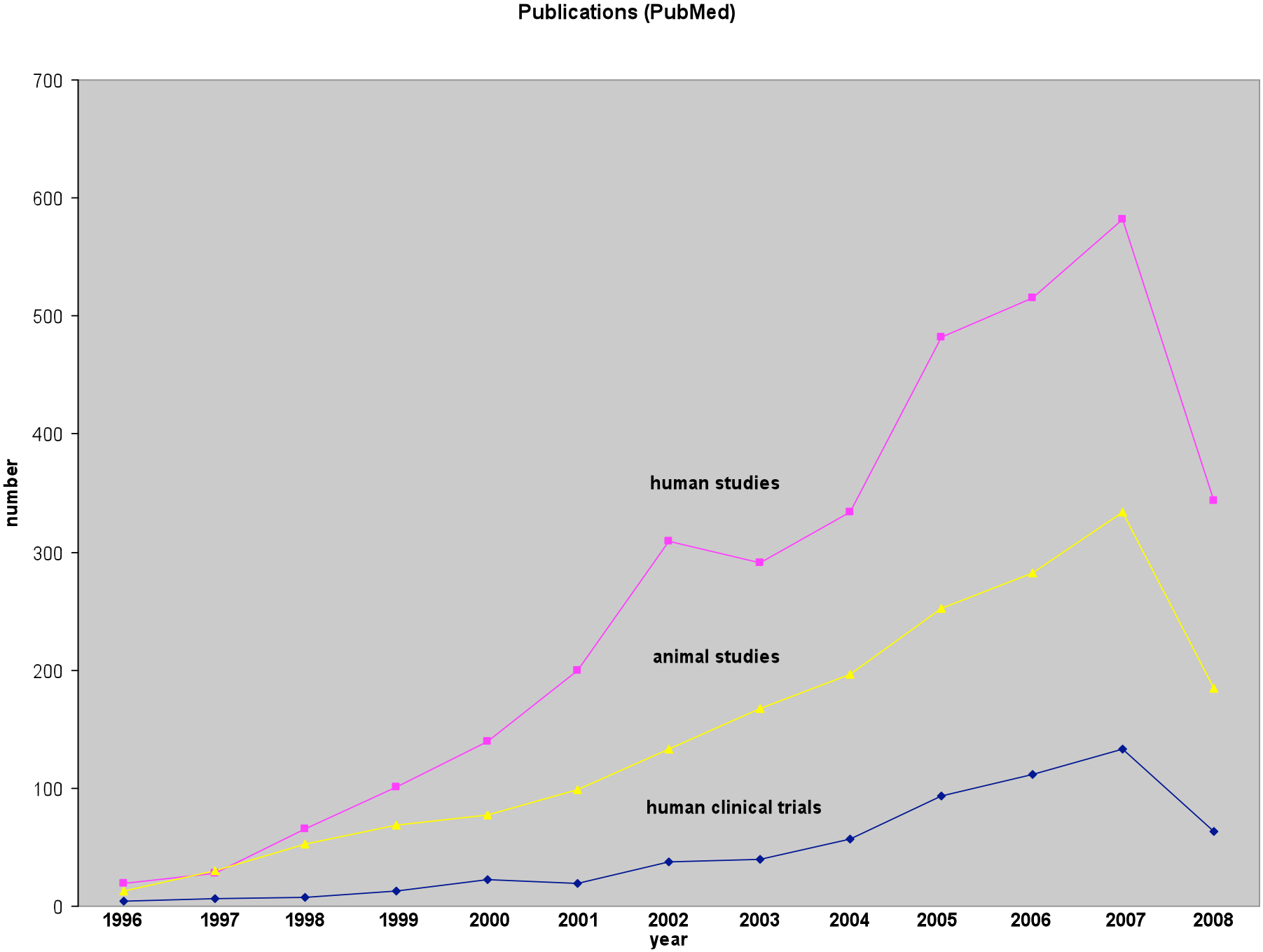


ISI Web of Science

Probiotic (s) in title. Publications by year



ISI Web of Science
Probiotic (s) in title being cited by year


Publications (PubMed)
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500
400
300
200
100
0
number
human studies
animal studies
human clinical trials
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
year

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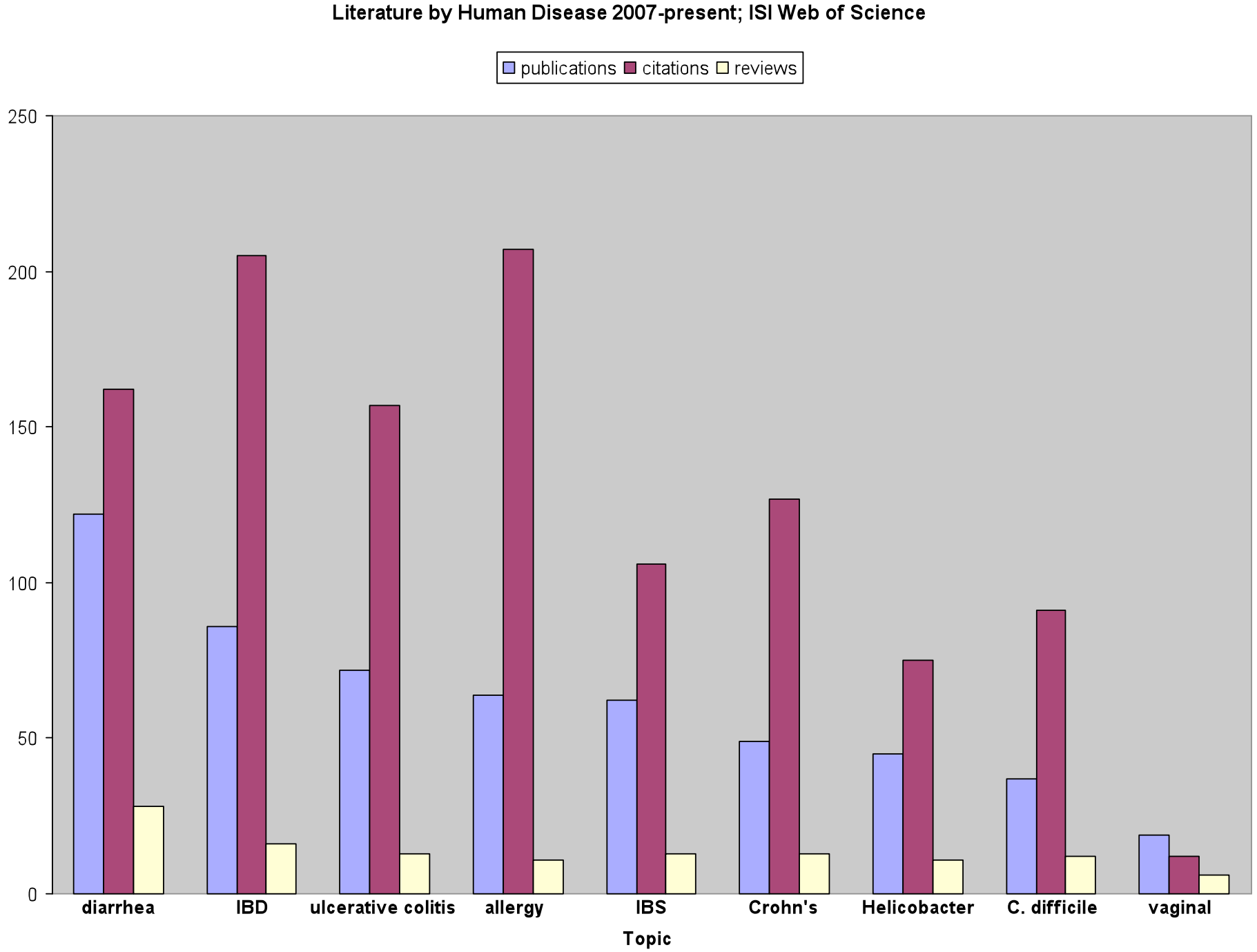
Literature by Human Disease 2007-present; ISI Web of Science
publications
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reviews
250
200
150
100
50
0
diarrhea
IBD
ulcerative colitis
allergy
IBS
Crohn's
Helicobacter
C. difficile
vaginal
Topic

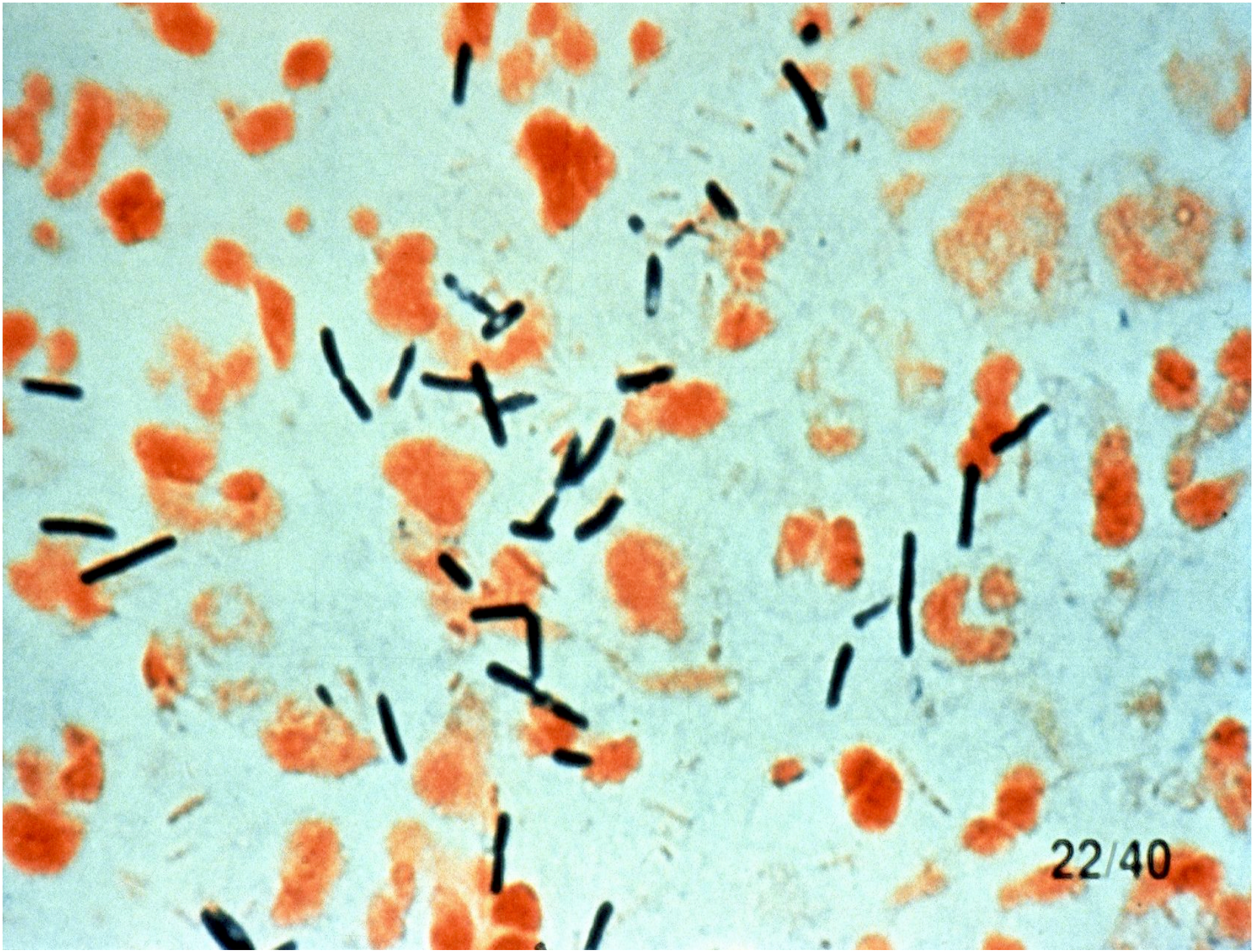
Meta-Analyses of Probiotic Treatments (2005 to present)

Disease	year	n	result	ref
IBS	2008	20	0.77 (improvement)	1
Nec. enterocolitis	2008	9	0.32 (prevention)	2
Ped. atopic dermatitis	2008	6	0.69 (prevention	3
Pediatric allergy and food sens.	2008	5	Promise but data lacking	4
Pouchitis	2008	5	0.04	5
Traveler's diarrhea	2007	5	Promise but data lacking	6
Traveler's diarrhea	2007	12	0.85	7
Preterm labor	2007	2	Data lacking[1]	8
H. pylori eradication (+antibiotics)	2007	14	1.84	9
H. pylori eradication adverse effects	2007	14	0.44	9
Antibiotic diarrhea (pediatric)	2006	6	0.43	10
Antibiotic diarrhea (pediatric)	2006	6	0.44	11
Antibiotic diarrhea	2006	25	0.43	12
C. difficile disease	2006	6	0.59	12
Crohn's disease	2006	7	Data lacking[2]	13
Acute diarrhea	2006	28	0.65	14

1. Vaginal infections decreased, however (GWE)
2. Results promising for E. coli Nissle and Saccharomyces boulardii, however (GWE)

References for previous slide showing Meta-Analyses of Probiotic Treatments (2005 to present)

1. McFarland LV, Dublin S. Meta-analysis of probiotics for the treatment of irritable bowel syndrome.World J Gastroenterol. 2008 May 7;14(17):2650-61.
2. Alfaleh K, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD005496.
3. Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. J Allergy Clin Immunol. 2008 Jan;121(1):116-121.
4. Osborn DA, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006475.
5. Elahi B, Nikfar S, Derakhshani S, Vafaie M, Abdollahi M. On the benefit of probiotics in the management of pouchitis in patients underwent ileal pouch anal anastomosis: a meta-analysis of controlled clinical trials. Dig Dis Sci. 2008 May;53(5):1278-84.
6. Takahashi O, Noguchi Y, Omata F, Tokuda Y, Fukui T. Probiotics in the prevention of traveler's diarrhea: meta-analysis. J Clin Gastroenterol. 2007 Mar;41(3):336-7.
7. McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhea. Travel Med Infect Dis. 2007 Mar;5(2):97-105.
8. Othman M, Neilson JP, Alfirevic Z. Probiotics for preventing preterm labour. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD005941.
9. Tong JL, Ran ZH, Shen J, Zhang CX, Xiao SD. Meta-analysis: the effect of supplementation with probiotics on eradication rates and adverse events during Helicobacter pylori eradication therapy. Aliment Pharmacol Ther. 2007 Jan 15;25(2):155-68.
10. Johnston BC, Supina AL, Vohra S. Probiotics for pediatric antibiotic-associated diarrhea: a meta-analysis of randomized placebo-controlled trials. CMAJ. 2006 Aug 15;175(4):377-83.
11. Szajewska H, Ruszczyński M, Radzikowski A. Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. J Pediatr. 2006 Sep;149(3):367-372.
12. McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease. Am J Gastroenterol. 2006 Apr;101(4):812-22.
13. Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD004826.
14. Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. Lancet Infect Dis. 2006 Jun;6(6):374-82.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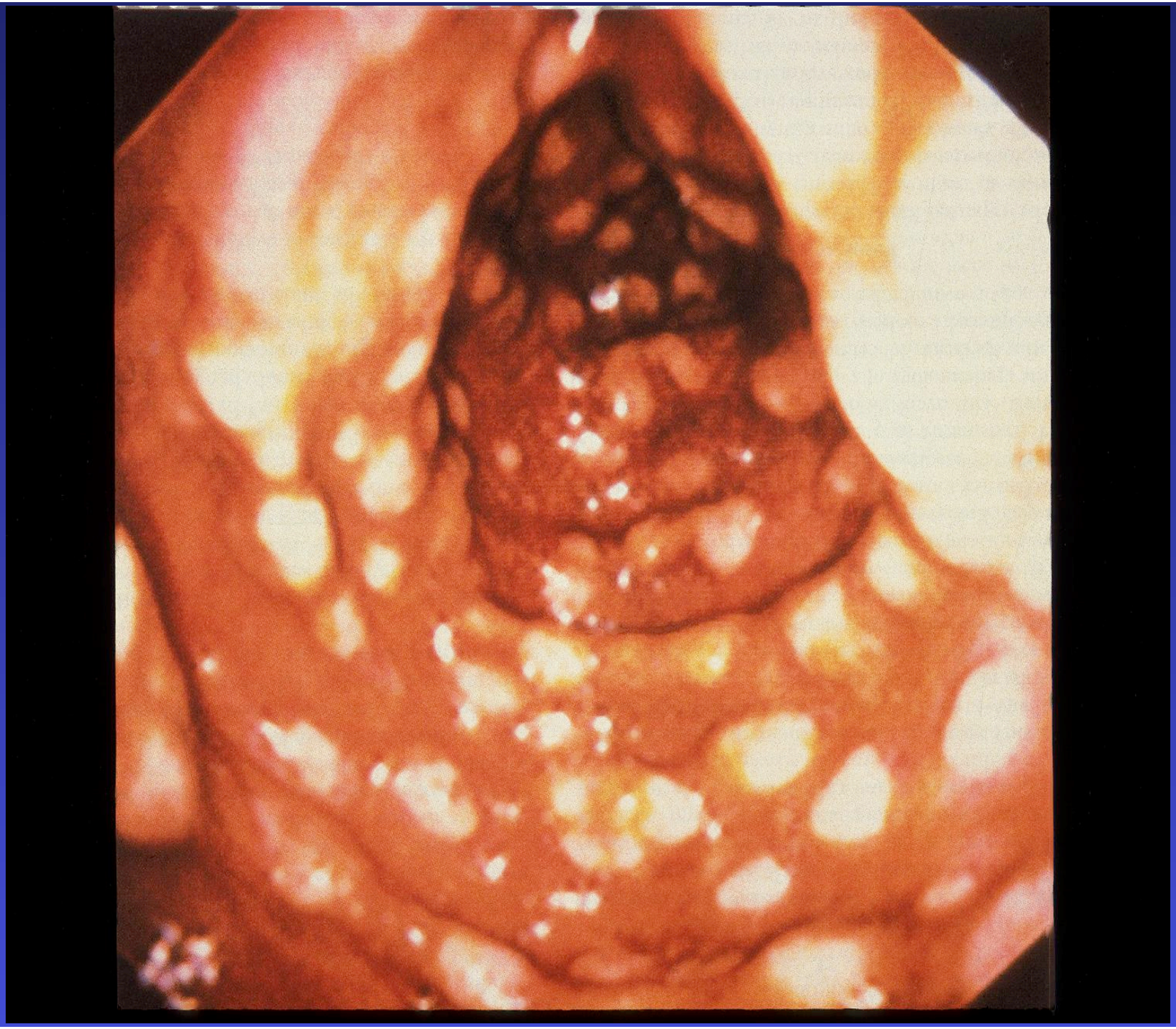
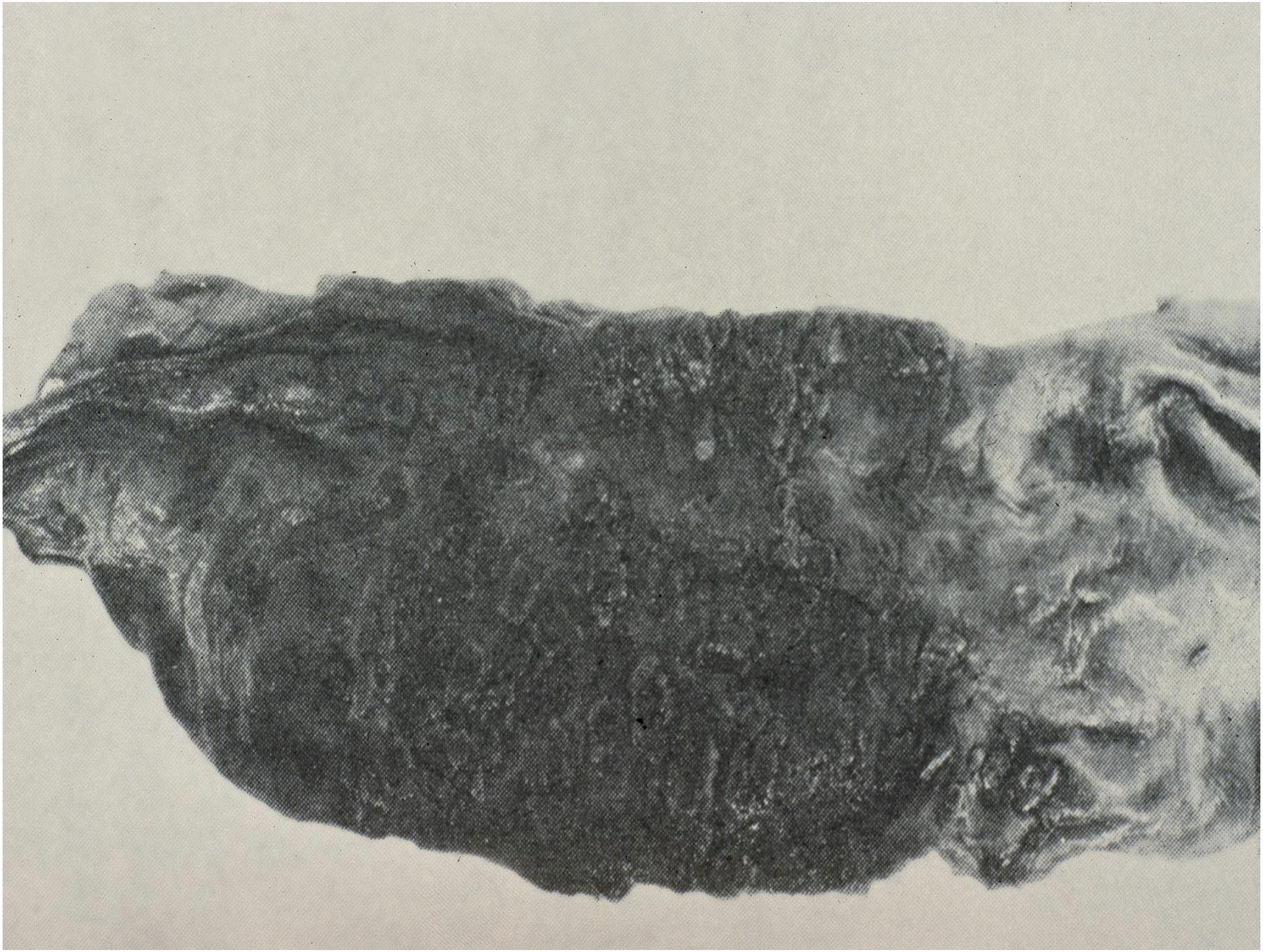
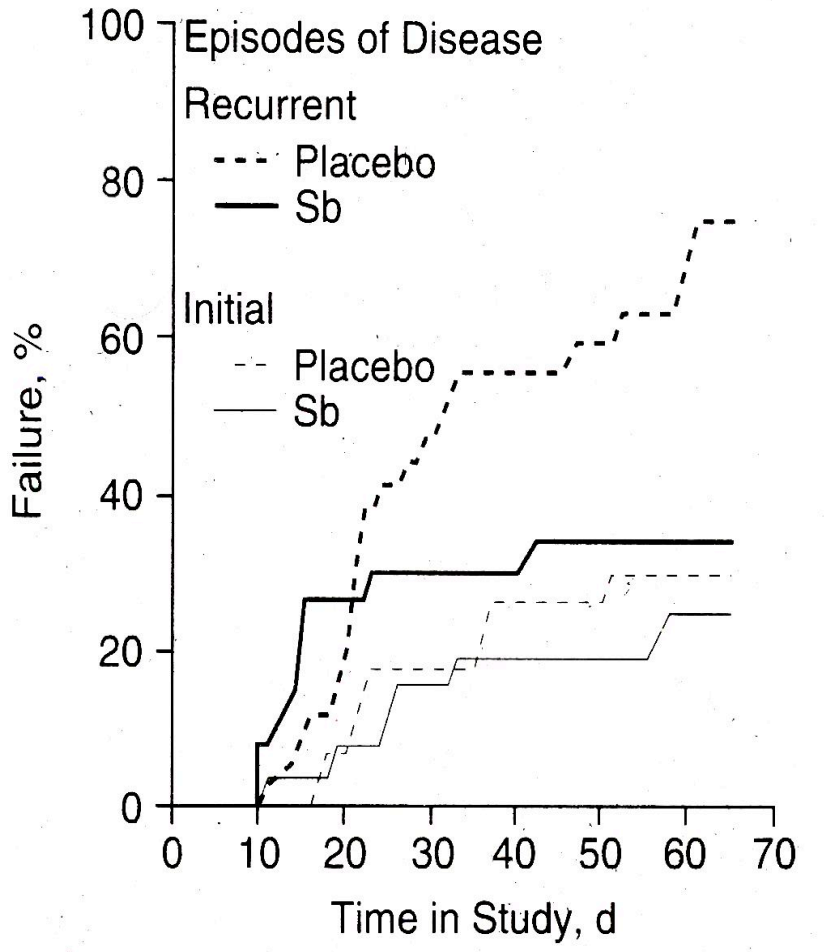


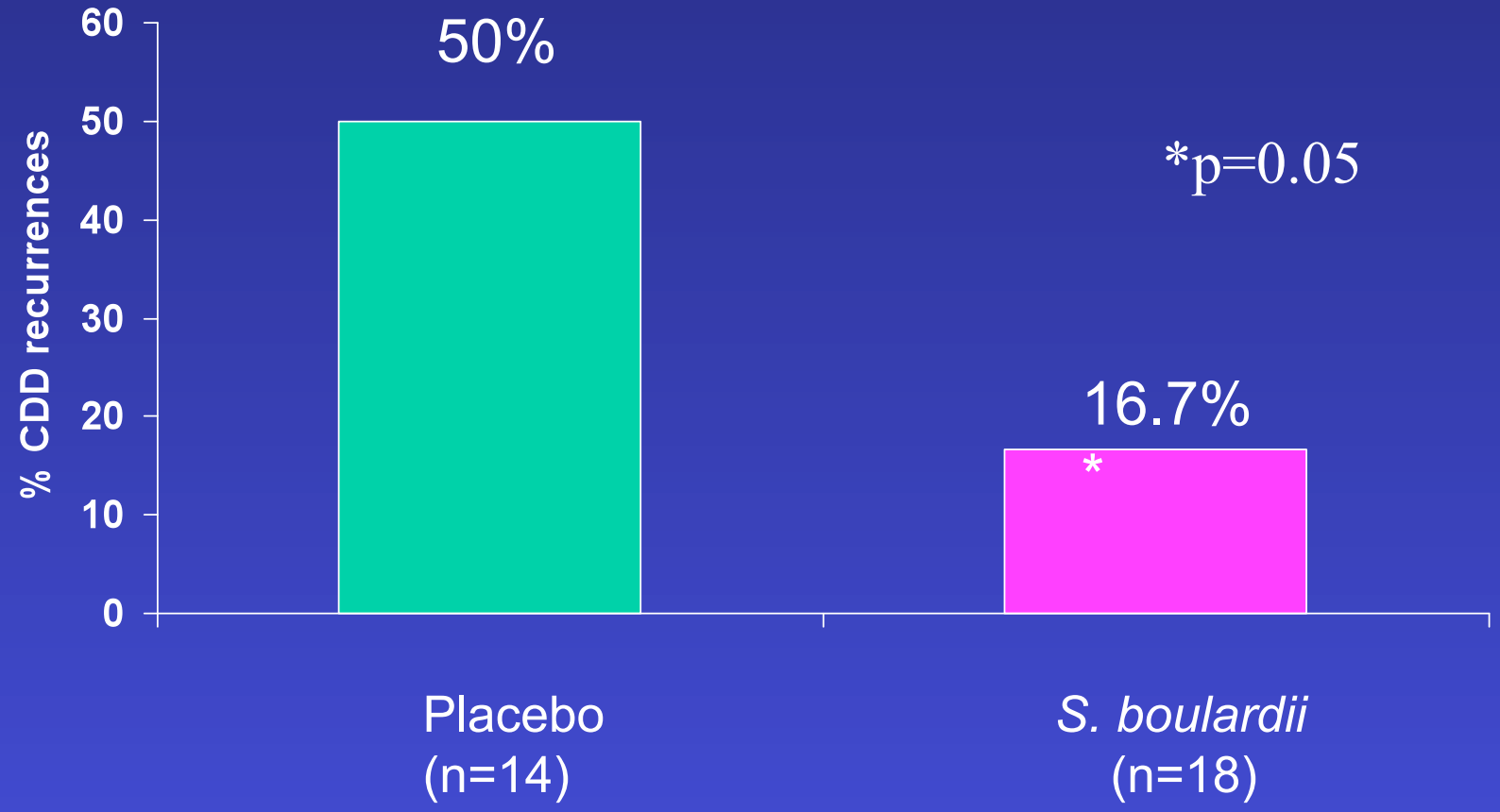


McFarland et al., JAMA; **271**, 1913-1918, (1994).



Kaplan-Meier failure curve for the probability of *Clostridium difficile* disease recurrence. Sb indicates *Saccharomyces boulardii.*

S. boulardii & High Dose Vancomycin for Recurrent *C. difficile* Disease



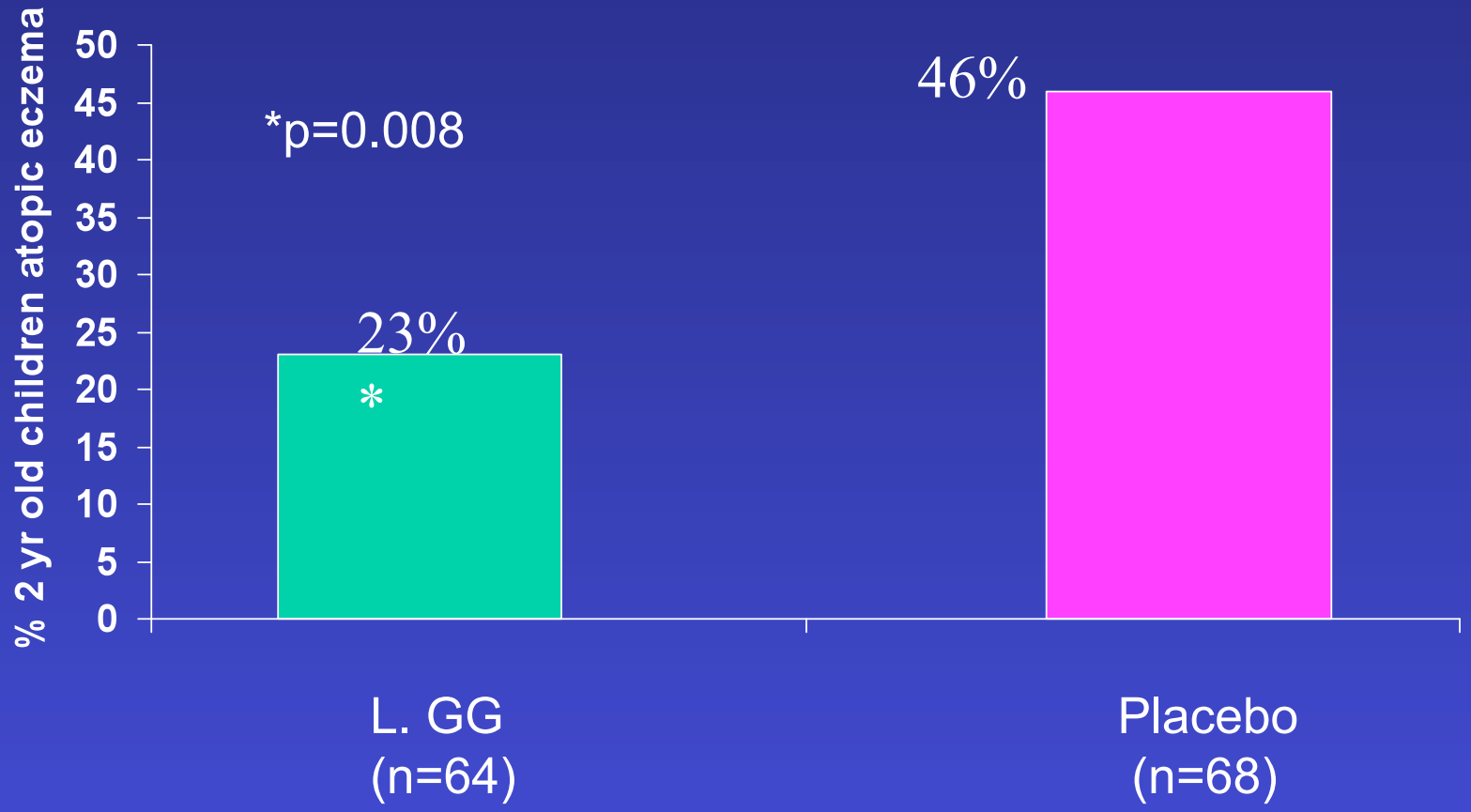
Surawicz CM. Clin Infect Dis 2000;31:1012-7.

Lactobacillus GG to Prevent Infantile Atopic Disease

- DBPC in Finland
- Family history atopic disease (eczema, allergic rhinitis, asthma)
- Mothers randomized:
  - *Lactobacillus* GG (1 x 10^{10} CFU/d)
  - Placebo
- Mothers treated 2-4 weeks before delivery
  Infants treated for 6 months
- Followed for 2 years

Kalliomaki M. Lancet 2001;357:1076-9

Lactobacillus GG and Infantile Atopic Disease [Results]



Kalliomaki M. Lancet 2001;357:1076-9

Myths about Probiotics

- Not well studied
- Are narrow spectrum agents for diarrhea only
- Not well regulated (partly true)
- Cultures are all therapeutically similar
- Optimum therapeutic dose is about 1 billion CFU

Consumerlab.com findings (11/16/09)

- 8/24 products tested did not meet labeled claim of potency or at least 1 billion CFU per recommended dose
- No findings of contamination with unwanted bacteria or molds

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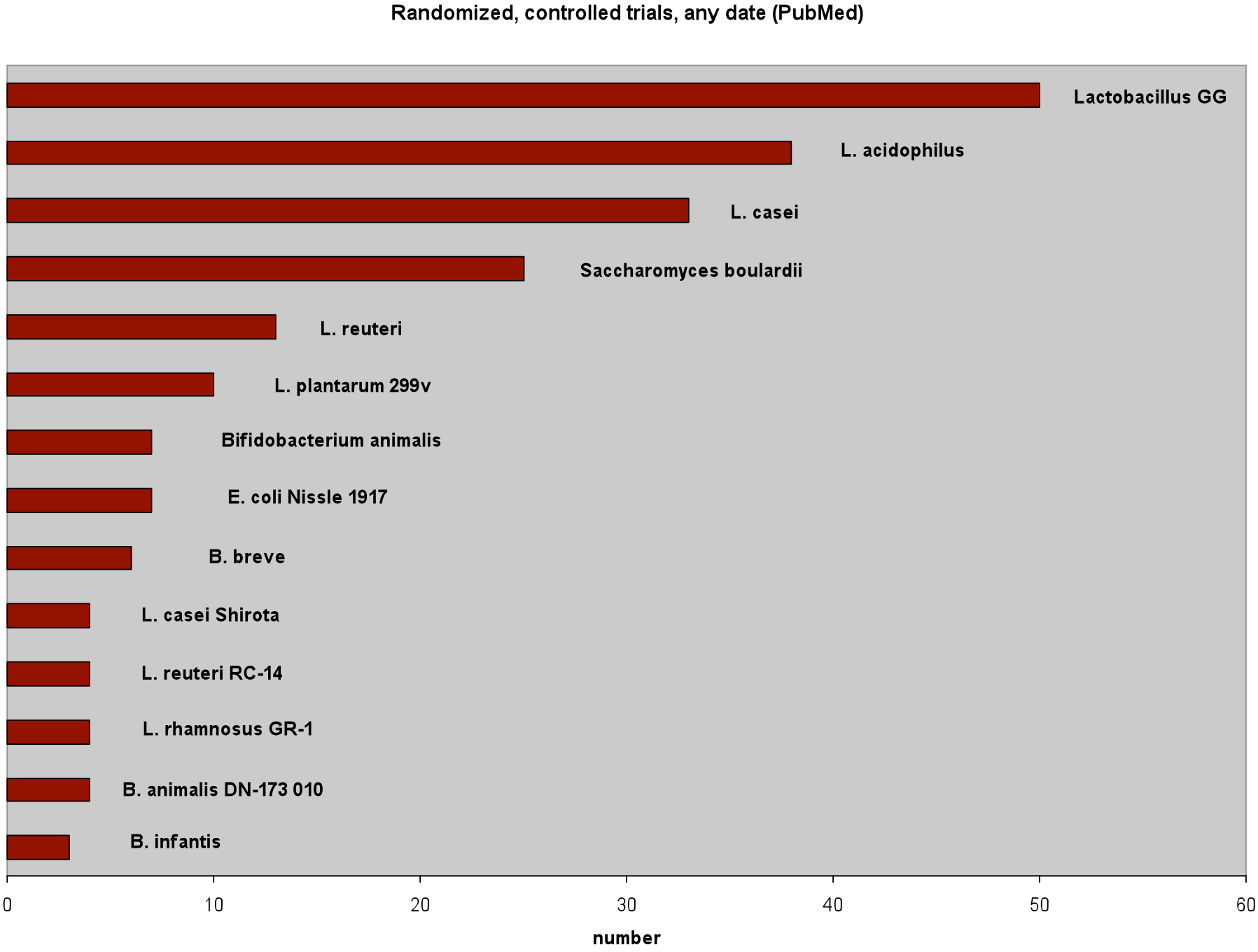
Randomized, controlled trials, any date (PubMed)
Lactobacillus GG
L. acidophilus
L. casei
Saccharomyces boulardii
L. reuteri
L. plantarum 299v
Bifidobacterium animalis
E. coli Nissle 1917
B. breve
L. casei Shirota
L. reuteri RC-14
L. rhamnosus GR-1
B. animalis DN-173 010
B. infantis
0
10
20
30
40
50
60
number

Table 6.1. Controlled clinical trials evaluating probiotics and Crohn's disease (from Elmer et al. The Power of Probiotics, Haworth Press 2007)

Probiotic	N	Result	Ref
L. rhamnosus GG	45	10.5% placebo 16.6% LGG, ns	Prantera [7]
L. rhamnosus GG	11	2/4 relapse placebo 3/5 relapse LGG, ns	Schultz [8]
Saccharomyces boulardii	17	4.6 stools/day placebo 3.3 stools/day in Sb*	Plein [9]
Saccharomyces boulardii	32	6/16 relapse in mesalamine 1/16 relapse in mesalamine/Sb	Guslandi [10]
E. coli Nissle 1917	28	7/12 relapse in prednisone 4/12 relapse in prednisone/Ec	Malchow [11]

* probiotic significantly better than control, $p<0.05$; ns=probiotic not significantly different than control

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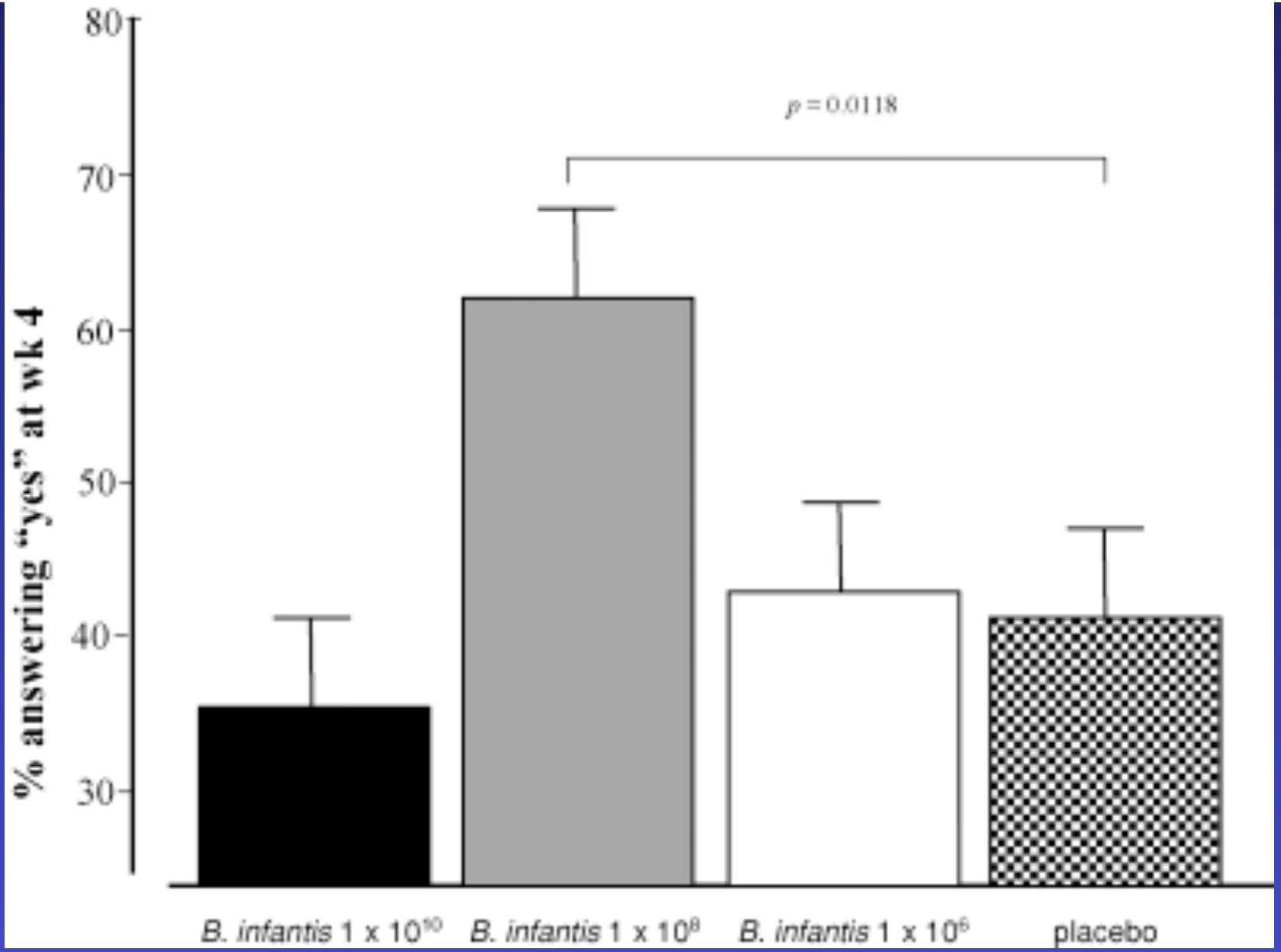
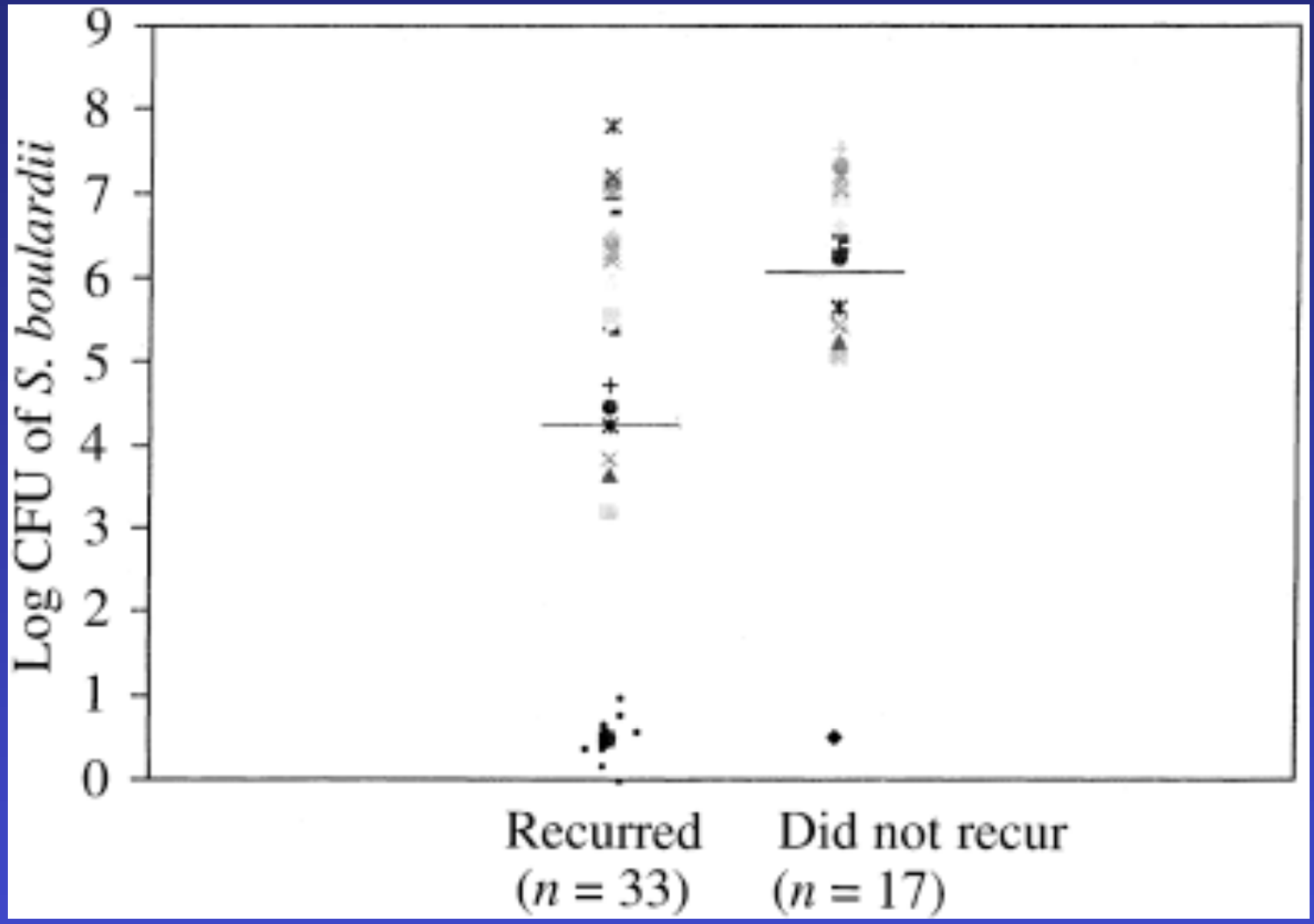


Whorwell et al. Am J Gastroenterol 2006;101:1581-1590. n=362 Q=relief?

Needed Directions

- Focus on therapeutic uses other than diarrhea
- Mechanisms of action determined
- Better appreciation of strain selection
- Recombinant strains to optimize
- Dose response data needed
- Effect of disease on dose needed
- Effect of diet
- Dose timing optimization needed
- Optimize drug delivery
- Research funding by governments and nonprofits

S. boulardii in patients with C. difficile disease



Elmer et al. Aliment Pharmacol Ther 1999;13:1663-1668.

$<10^4$ 14/15 (93%) recurred; $>10^4$ 19/35 (54%)

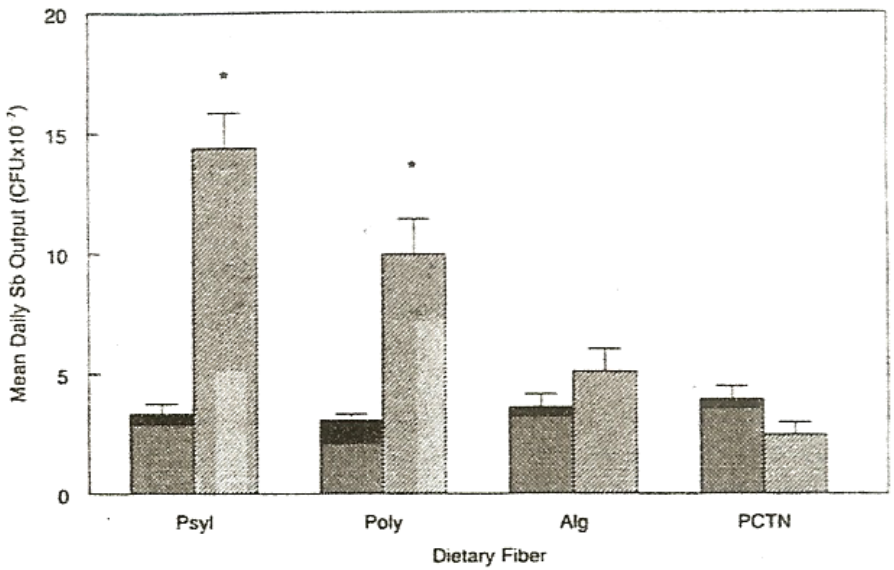


Fig. 1. Effect of dietary fiber on *S. boulardii* steady state levels in the rat. * = $p < 0.001$ compared to fiber-free controls. Hatched = fiber-free controls, striped = fiber (psyl = psyllium hydrocolloid, poly = polycarbophyl, alg = alginic acid, Pctn = pectin). n = 6–8 per group.

Potential Advantages and Disadvantages of Probiotics

Advantages

- Multiple Mechanisms of Action
- Resistance is Infrequent
- Use May Reduce Exposure to Antibiotics
- Delivery of Microbial Enzymes
- Well Tolerated
- Benefit to Risk Ration is Favorable

Disadvantages

- Persistence Possible
- Translocation Possible
- Transfer of Resistance Plasmids?
- Infection Possible
- Quality Control Issues
- Regulatory Issues in USA

Evidence supporting commercially available (USA) probiotics*

condition	VSL#3	L. reueri	LGG	Sb
AAD	Uneven	Good	Good	Good
Acute Adult	NA	NA	Good	Good
Acute pediatric	NA	NA	Good	Good
Traveler diarrhea	NA	NA	Fair	Fair
C. dif	NA	NA	Limited	Good
IBS	Fair	NA	None	NA
Crohns	NA	NA	None	Fair
UC	Fair	NA	NA	Fair

NA=not available (no studies), None=negative studies

Conclusions

1. Enhanced funding for basic research on probiotics badly needed

2. It is time for optimization of existing therapies with proven probiotics

5. Exploration needed of new applications for probiotics

6. Improved regulatory oversight of commercial products

7. OTC status granted for some well studied probiotics

Homeopathic Products

- Principle of analogy or Law of Similars
- Small or infinitesimal doses (3X-30C)
  - Avogadro's number=$6x10^{23}$ = ~23X
- Succession and potentization (see http://www.boiron.com/en/htm/02_medi_homeo/prepa_medi.htm)
- Ultra-high dilution effects
- Final product
- World Market
- USA

Evidence??

- In vitro studies
- Animal studies
- Human studies
- Meta-analyses of human studies
- Implausibility, entrenched skeptics and overenthusiastic zealots

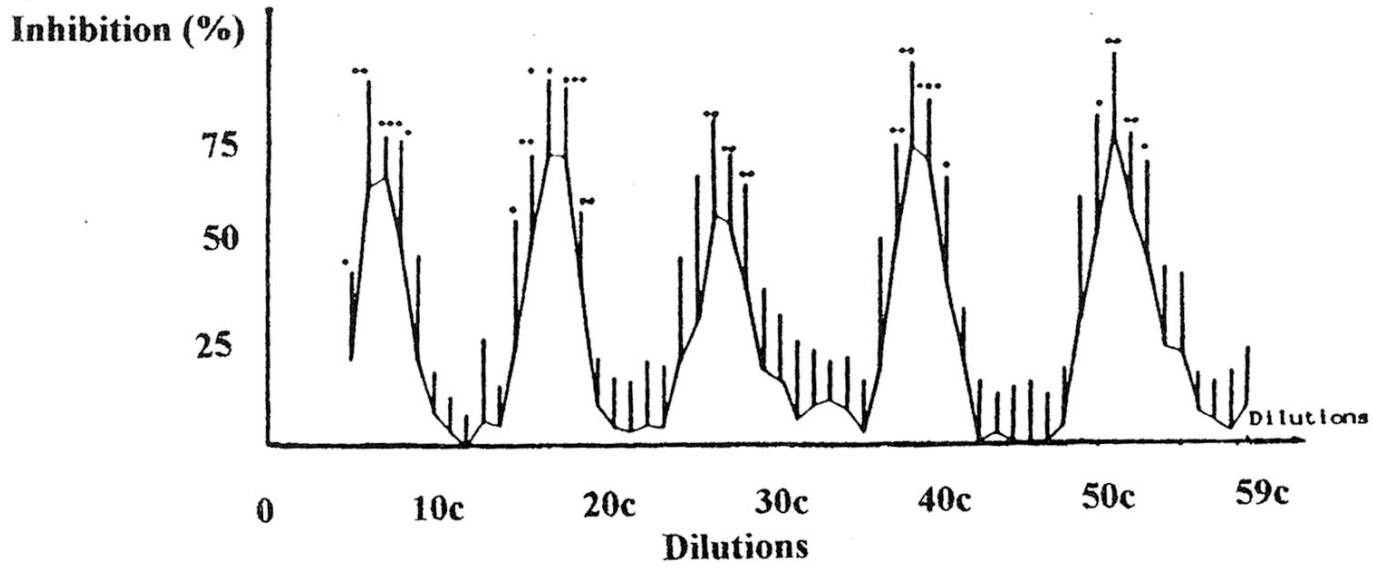
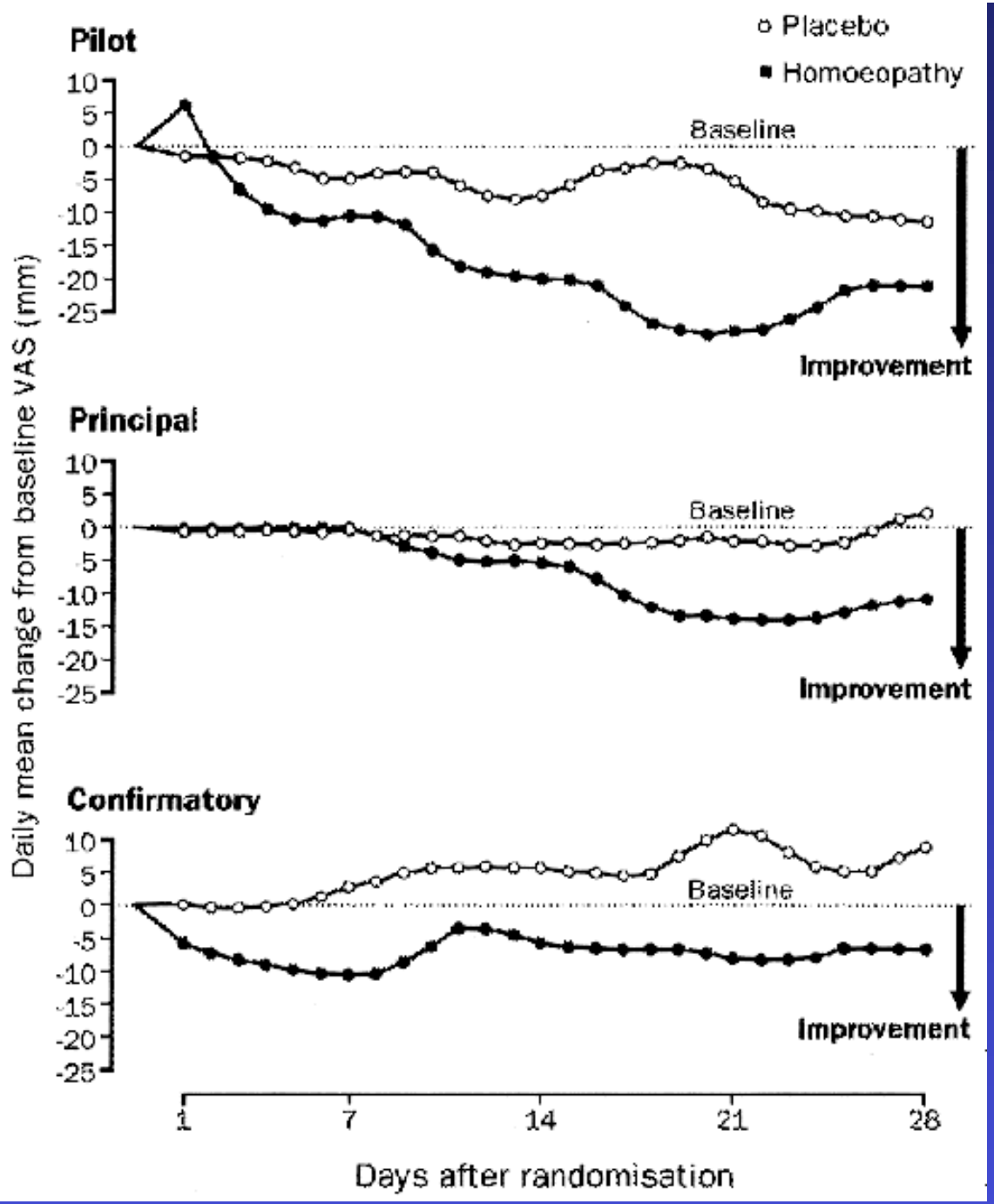


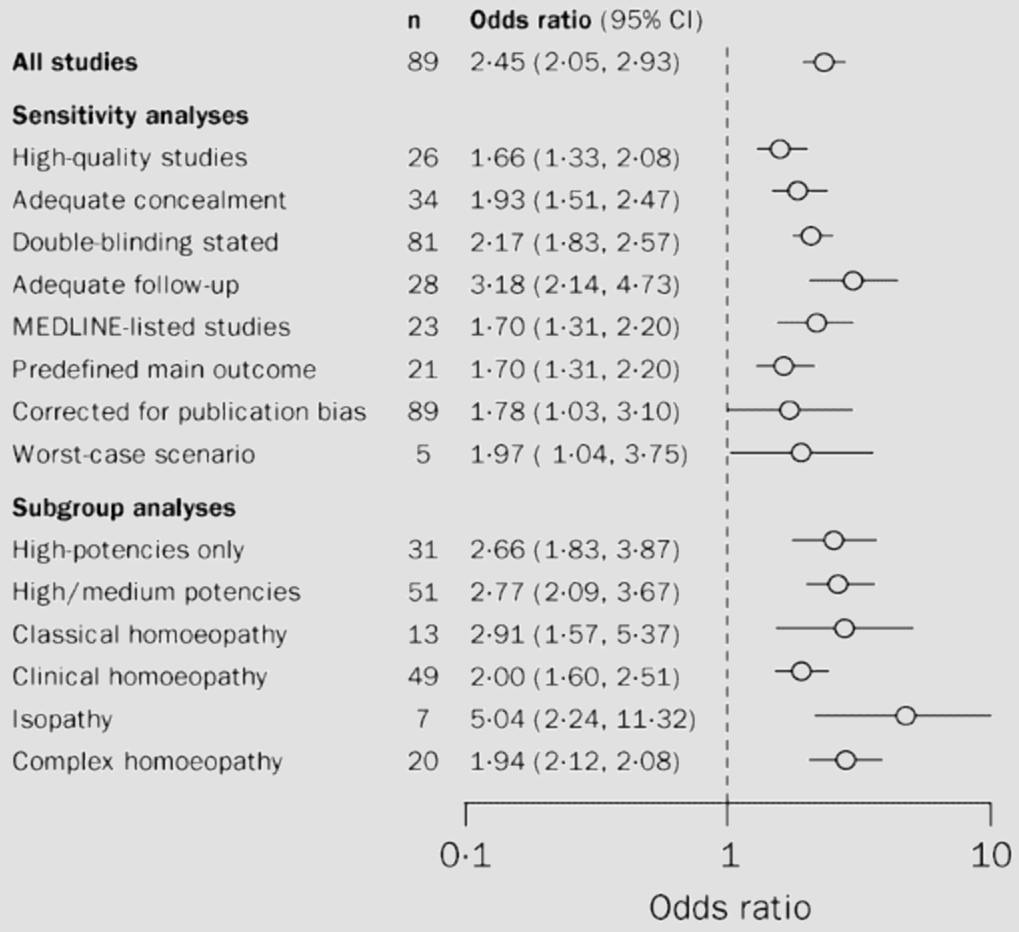
FIG. 8. Inhibition of basophil degranulation by successive dilutions of histamine. An oscillation of inhibititory activity across the series of histamine dilutions is notable. The results are expressed in mean percentages of inhibition ± S.E.M. on 10 experiments. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$. In: Sainte-Laudy et al., 1991. Permission to reproduce this figure has been kindly granted by Taylor & Francis.

In: Vallance AK. J Alt Compl Med 1998;4:49-76.

Reilly et al. Lancet 1994;344:1601-06

asthma





Linde et al. Lancet. 1997 Sep 20;350(9081): 834-43 .

TABLE 2. Results in three studies of homeopathy for childhood diarrhea and combined results, with all children completing 5-day follow-up

Variable	Treatment	Control	*P*
Nicaragua, 1990	(*n* = 16)	(*n* = 17)	
Duration of diarrhea	2.4 ± 1.7*	3.0 ± 1.6	0.28
No. of stools/day	2.8 ± 1.8	3.5 ± 1.4	0.57
Nicaragua, 1991	(*n* = 40)	(*n* = 41)	
Duration of diarrhea	3.0 ± 1.9	3.8 ± 1.7	0.048
No. of stools/day	2.2 ± 1.7	2.9 ± 2.0	0.07
Nepal	(*n* = 64)	(*n* = 52)	
Duration of diarrhea	3.5 ± 2.0	4.2 ± 1.9	0.06
No. of stools/day	3.0 ± 2.2	3.7 ± 2.0	0.03
Combined	(*n* = 120)	(*n* = 110)	
Duration of diarrhea	3.1 ± 2.0	3.8 ± 1.9	0.008
No. of stools/day	2.7 ± 2.0	3.4 ± 2.0	0.004

* Mean ± SD.

Jacobs et al. Pediatr Infect Dis J. 2003;22:229-34.

TABLE 1. COMMON HOMEOPATHIC REMEDIES FOR ACUTE DIARRHEA AND THEIR INDICATIONS

Arsenicum album (arsenic trioxide)

Mind:	**Great anxiety and restlessness.** Tossing about in bed. Fearful, doesn't want to be alone.
General:	Prostration. **Worse after midnight.** Burning heat with thirst for small amounts. Chilly, better being covered, cold sweats. Vomiting immediately after eating or drinking.
Stools:	**Acrid, burning, excoriating.** Diarrhea worse at night, after midnight. Putrid, bloody, odor of rotton eggs.

Chamomilla (German chamomile)

Mind:	Capricious; irritable; quarrelsome, nothing pleases. **Asks for something, then rejects it,** striking out, sensitive to pain; moaning; frenzied. **Better being carried.**
General:	One cheek red, other pale; hot; worse from heat, better from cold drinks. Worse evening, until midnight.
Stools:	Green, slimy, offensive, like chopped grass. **Diarrhea during teething.** Smelling like rotten eggs; colic with diarrhea, better after stool.

Calcarea carbonica (calcium carbonate)

Mind:	Slow, lethargic, fears the dark and being alone.
General:	**Profuse perspiration on the head during sleep.** Sour smell to perspiration. Strong desire for milk, eggs, and indigestibles (pica). Plump children who get sick frequently and have swollen glands.
Stools:	**Sour odor to the stools.** Diarrhea during teething. Watery with bits of undigested food.

Podophyllum (May-apple)

Mind:	Diarrhea after mental excitement. Figety and restless.
General	Gagging or empty retching. Violent cramps of the feet, calves, and thighs. Head sweats during sleep. **Thirst for large quantities of cold water.**
Stools:	**Profuse, frequent, gushing, painless, watery.** Bloody with green mucus, very offensive. **Rectal prolapse.** Exhaustion after stool. Diarrhea during teething, after fruit.

Sulphur (flowers of sulphur)

Mind:	Irritable, indifferent, weeping.
General	Cold sweat on face and feet. Blue circles under eyes, weakness. Thirsty for cold drinks, little appetite.
Stools:	Diarrhea worse at night, after milk; involuntary, sudden expulsion. **Worse 5:00 a.m. Red ring around anus.** Offensive, acrid stools. Painless; sour; thin; watery. **Odor of rotten eggs.**

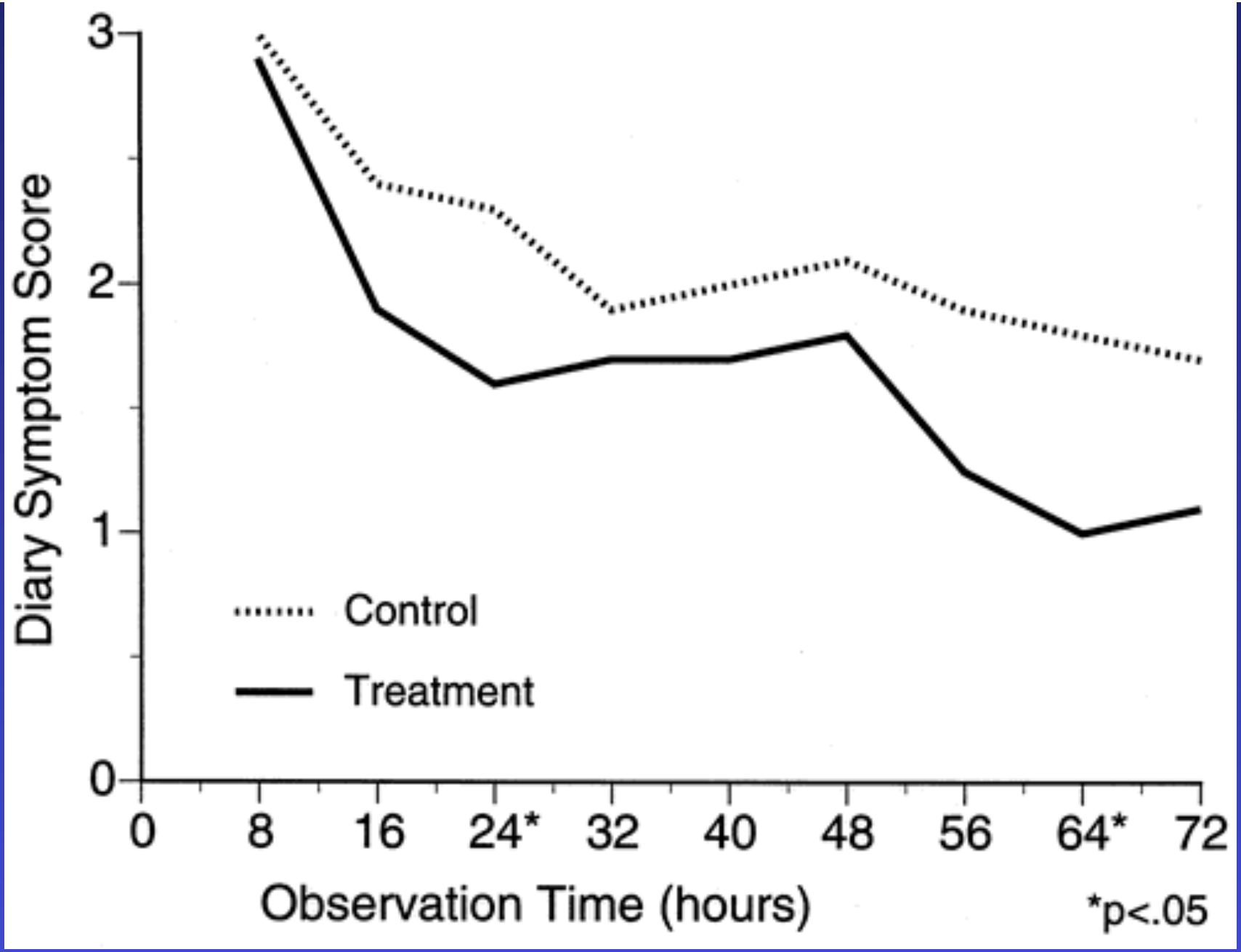
Bold type indicates the most important symptoms for each medicine.
Sources: Bell, 1888; Boericke, 1971.

Jacobs et al. J Alt Compl Med 2000;6:131-139 n=126 in Nepal

TABLE 1. Indications for common homeopathic medicines for acute otitis media[9]

Pulsatilla (windflower)	
Mind:	**Weepy, clingy, whiney**. Wants to be held and carried. **Changeable moods**. Needs attention and reassurance.
Generals:	Worse in a warm room, **better from fresh air. Thirstless**.
Ears:	**Earache comes on in middle of the night**. External ear and meatus is red. Decreased hearing. Earache following a cold
Chamomilla (German chamomile)	
Mind:	Capricious; irritable; quarrelsome, nothing pleases. **Asks for something, then rejects it**, striking out, sensitive to pain; moaning; frenzied. **Better being carried.**
Generals:	One cheek red, other pale; hot; thirsty for cold drinks. Worse evening, until midnight. Night sweats.
Ear:	**Unbearable pain, screaming from pain**. Ears feel stopped.
Sulfur (elemental sulfur)	
Mind:	Emotionally irritable and sluggish.
Generals:	**Worse from heat**. Fever with sweating and shivering. Restless sleep. Doesn't want to wash or bathe. **Thirsty for cold drinks**, little appetite. **Worse 5 a.m.**
Ear:	**Sharp pains, worse on the left**. Redness of external ear. Enlarged cervical lymph nodes. Earache with painful ringing in the ears.
Calcarea carbonica (calcium carbonate)	
Mind:	Irritable, **stubborn**, complaining. Fearful at night.
Generals:	**Sweaty head and back of the neck**, especially at night. Sour odor to sweat, stools, breath. Sensitive to cold.
Ear:	**Throbbing, pulsating ear pain**, decreased hearing. Enlarged cervical lymph nodes.

Jacobs et al. Pediatr Infec Dis 2001;20:177-183. N=75



Jacobs et al. Pediatr Infec Dis 2001;20:177-183. N=75

http://homeopathicpharmacy.org/