# Pre- and Probiotics and gut health
# A review of the evidence

CAPGAN
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# Outline

- Definitions
- What evidence do we have that informs practice?
  - Prevention of antibiotic-associated diarrhoea
  - Treatment of acute diarrhoea
  - Prevention of NEC in preterm infants
  - Prevention of atopic eczema
- What are the challenges for the research community?

# Definitions

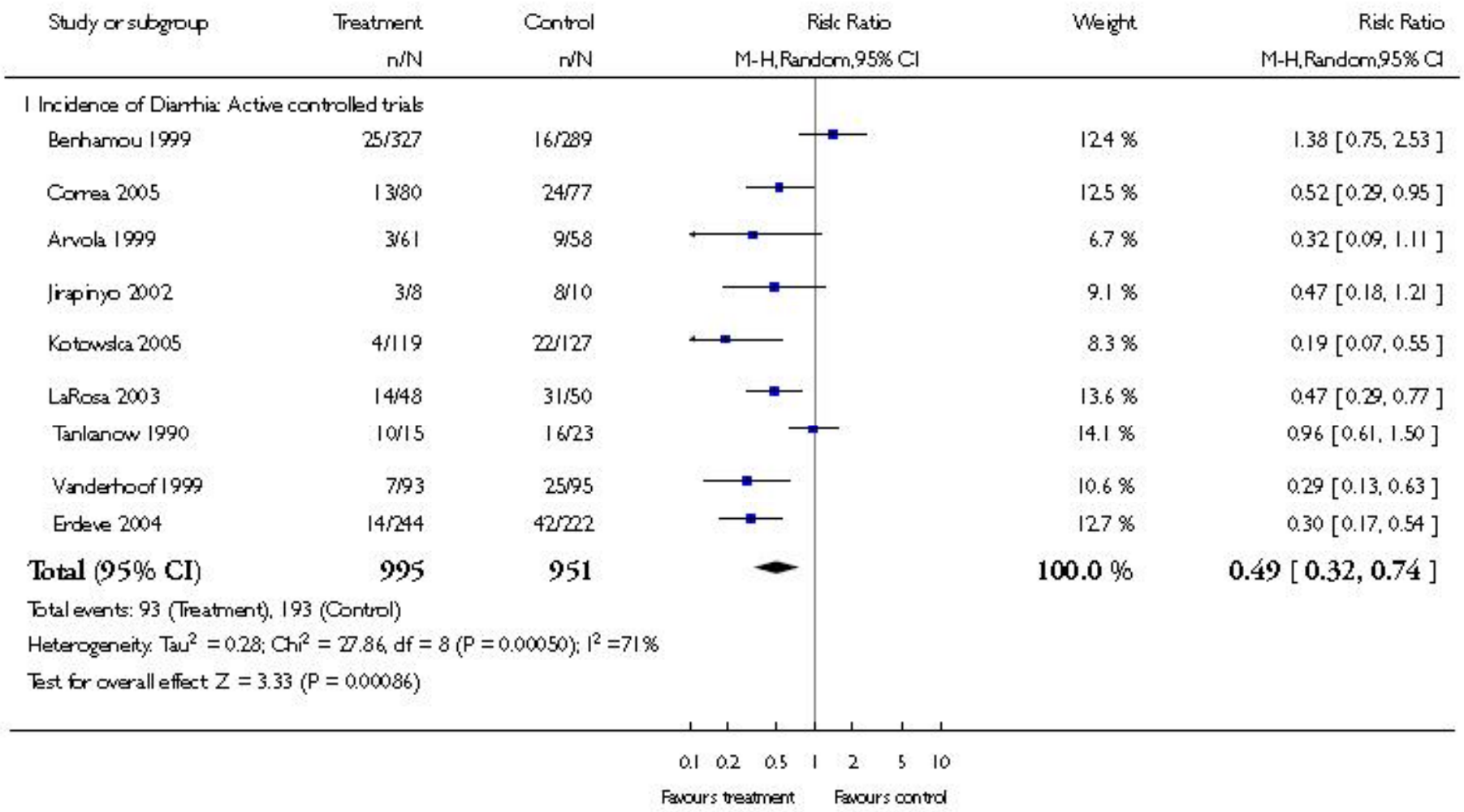
**Probiotic:** "live microorganisms which, when administered in adequate amounts, confer health benefits on the host"

**Prebiotic:** "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the GI microflora, that confers benefits upon host well-being and health."

**Synbiotic:** pre- + pro- biotic

**Functional food:** "health benefit beyond its nutrient content"

# Prevention of antibiotic associated diarrhoea



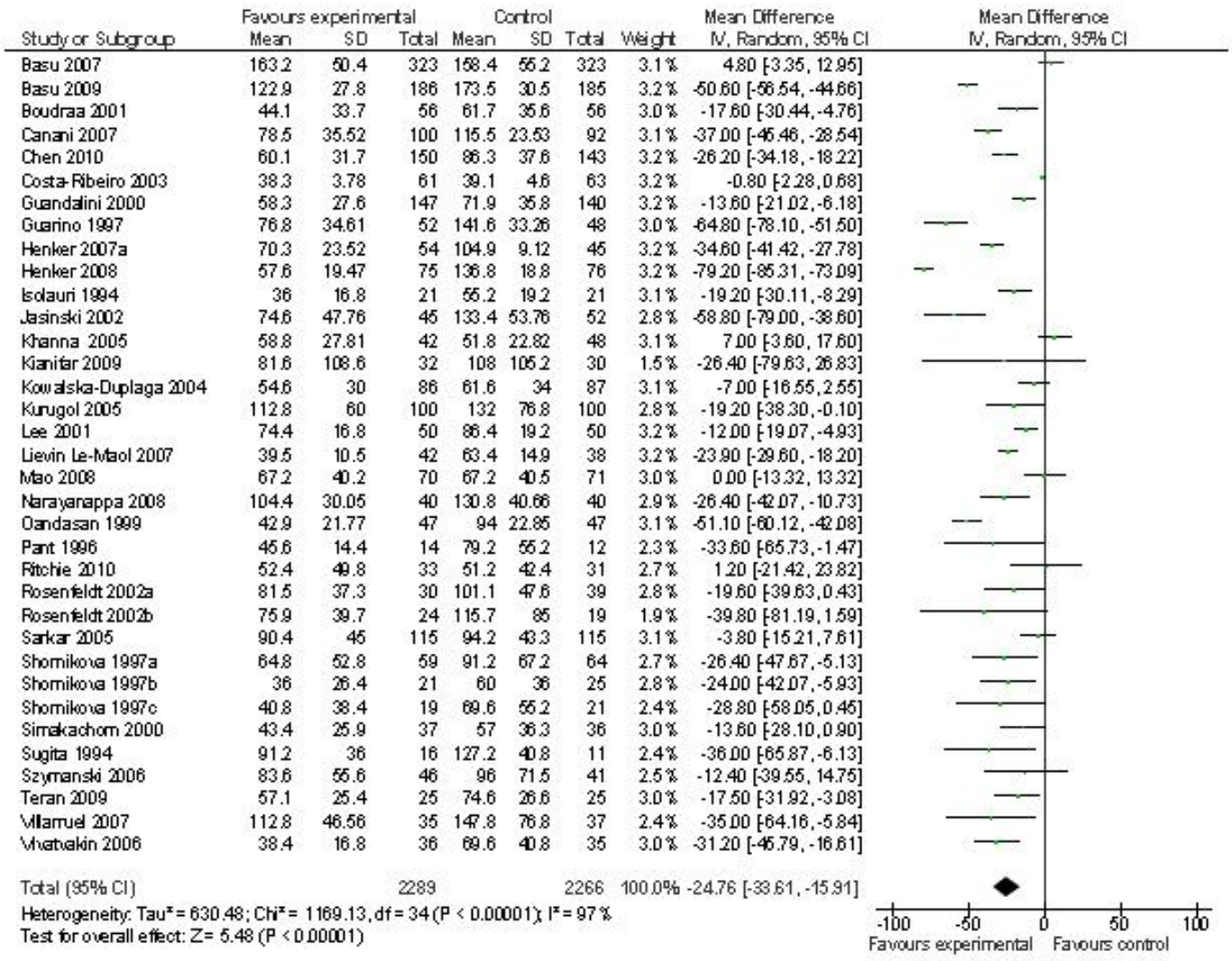

**Risk of AAD:** PP analysis (9 trials / 1946 infants/children)

Johnston et al. *Cochrane Database of Systematic Reviews 2008*

# Variability in probiotic regimens

| Reference | Probiotic | No. orgs/day | Duration admin |
|---|---|---|---|
| Correa 2005 | *B. lactis*<br>*S. thermophilus* | 825m | 15d |
| Jirapinyo 2002 | *L. acidophilus*<br>*B. infantis* | Unclear | 7d |
| Tankanow 1990 | *L. acidophilus*<br>*L. bulgaricus* | 2b | 5-12d |
| La Rose 2003 | *L. sporogenes*<br>FOS | 5.5b | 10d |
| Arvola 1999 | L. GG | 4b | Duration Ab treatment |
| Vanderhoof 1999 | L. GG | 10-20b ~weight | Duration Ab treatment |
| Kotowska 2005 | *S. boulardii* | 10b | Duration Ab treatment |
| Benhamou 1999 | *S. boulardii* | 4.5b | unclear |
| Erdeve 2004 | *S. boulardii* | 5b | unclear |

# Treatment of acute diarrhoea



| Study or Subgroup | Favours experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Basu 2007 | 163.2 | 50.4 | 323 | 158.4 | 55.2 | 323 | 3.1% | 4.80 [-3.35, 12.95] |
| Basu 2009 | 122.9 | 27.8 | 186 | 173.5 | 30.5 | 185 | 3.2% | -50.60 [-56.54, -44.66] |
| Boudraa 2001 | 44.1 | 33.7 | 56 | 61.7 | 35.6 | 56 | 3.0% | -17.60 [-30.44, -4.76] |
| Canani 2007 | 78.5 | 35.52 | 100 | 115.5 | 23.53 | 92 | 3.1% | -37.00 [-45.46, -28.54] |
| Chen 2010 | 60.1 | 31.7 | 150 | 86.3 | 37.6 | 143 | 3.2% | -26.20 [-34.18, -18.22] |
| Costa-Ribeiro 2003 | 38.3 | 3.78 | 61 | 39.1 | 4.6 | 63 | 3.2% | -0.80 [-2.28, 0.68] |
| Guandalini 2000 | 58.3 | 27.6 | 147 | 71.9 | 35.8 | 140 | 3.2% | -13.60 [-21.02, -6.18] |
| Guarino 1997 | 76.8 | 34.61 | 52 | 141.6 | 33.26 | 48 | 3.0% | -64.80 [-78.10, -51.50] |
| Henker 2007a | 70.3 | 23.52 | 54 | 104.9 | 9.12 | 45 | 3.2% | -34.60 [-41.42, -27.78] |
| Henker 2008 | 57.6 | 19.47 | 75 | 136.8 | 18.8 | 76 | 3.2% | -79.20 [-85.31, -73.09] |
| Isolauri 1994 | 36 | 16.8 | 21 | 55.2 | 19.2 | 21 | 3.1% | -19.20 [-30.11, -8.29] |
| Jasinski 2002 | 74.6 | 47.76 | 45 | 133.4 | 53.76 | 52 | 2.8% | -58.80 [-79.00, -38.60] |
| Khanna 2005 | 58.8 | 27.81 | 42 | 51.8 | 22.82 | 48 | 3.1% | 7.00 [-3.60, 17.60] |
| Kianifar 2009 | 81.6 | 108.6 | 32 | 108 | 105.2 | 30 | 1.5% | -26.40 [-79.63, 26.83] |
| Kowalska-Duplaga 2004 | 54.6 | 30 | 86 | 61.6 | 34 | 87 | 3.1% | -7.00 [-16.55, 2.55] |
| Kurugol 2005 | 112.8 | 60 | 100 | 132 | 76.8 | 100 | 2.8% | -19.20 [-38.30, -0.10] |
| Lee 2001 | 74.4 | 16.8 | 50 | 86.4 | 19.2 | 50 | 3.2% | -12.00 [-19.07, -4.93] |
| Lievin Le-Maol 2007 | 39.5 | 10.5 | 42 | 63.4 | 14.9 | 38 | 3.2% | -23.90 [-29.60, -18.20] |
| Mao 2008 | 67.2 | 40.2 | 70 | 67.2 | 40.5 | 71 | 3.0% | 0.00 [-13.32, 13.32] |
| Narayanappa 2008 | 104.4 | 30.05 | 40 | 130.8 | 40.66 | 40 | 2.9% | -26.40 [-42.07, -10.73] |
| Oandasan 1999 | 42.9 | 21.77 | 47 | 94 | 22.85 | 47 | 3.1% | -51.10 [-60.12, -42.08] |
| Pant 1996 | 45.6 | 14.4 | 14 | 79.2 | 55.2 | 12 | 2.3% | -33.60 [-65.73, -1.47] |
| Ritchie 2010 | 52.4 | 49.8 | 33 | 51.2 | 42.4 | 31 | 2.7% | 1.20 [-21.42, 23.82] |
| Rosenfeldt 2002a | 81.5 | 37.3 | 30 | 101.1 | 47.6 | 39 | 2.8% | -19.60 [-39.63, 0.43] |
| Rosenfeldt 2002b | 75.9 | 39.7 | 24 | 115.7 | 85 | 19 | 1.9% | -39.80 [-81.19, 1.59] |
| Sarkar 2005 | 90.4 | 45 | 115 | 94.2 | 43.3 | 115 | 3.1% | -3.80 [-15.21, 7.61] |
| Shornikova 1997a | 64.8 | 52.8 | 59 | 91.2 | 67.2 | 64 | 2.7% | -26.40 [-47.67, -5.13] |
| Shornikova 1997b | 36 | 26.4 | 21 | 60 | 36 | 25 | 2.8% | -24.00 [-42.07, -5.93] |
| Shornikova 1997c | 40.8 | 38.4 | 19 | 69.6 | 55.2 | 21 | 2.4% | -28.80 [-58.05, 0.45] |
| Simakachorn 2000 | 43.4 | 25.9 | 37 | 57 | 36.3 | 36 | 3.0% | -13.60 [-28.10, 0.90] |
| Sugita 1994 | 91.2 | 36 | 16 | 127.2 | 40.8 | 11 | 2.4% | -36.00 [-65.87, -6.13] |
| Szymanski 2006 | 83.6 | 55.6 | 46 | 96 | 71.5 | 41 | 2.5% | -12.40 [-39.55, 14.75] |
| Teran 2009 | 57.1 | 25.4 | 25 | 74.6 | 26.6 | 25 | 3.0% | -17.50 [-31.92, -3.08] |
| Villarruel 2007 | 112.8 | 46.56 | 35 | 147.8 | 76.8 | 37 | 2.4% | -35.00 [-64.16, -5.84] |
| Vlietvakin 2006 | 38.4 | 16.8 | 36 | 69.6 | 40.8 | 35 | 3.0% | -31.20 [-45.79, -16.61] |
| Total (95% CI) | | | 2289 | | | 2266 | 100.0% | -24.76 [-33.61, -15.91] |

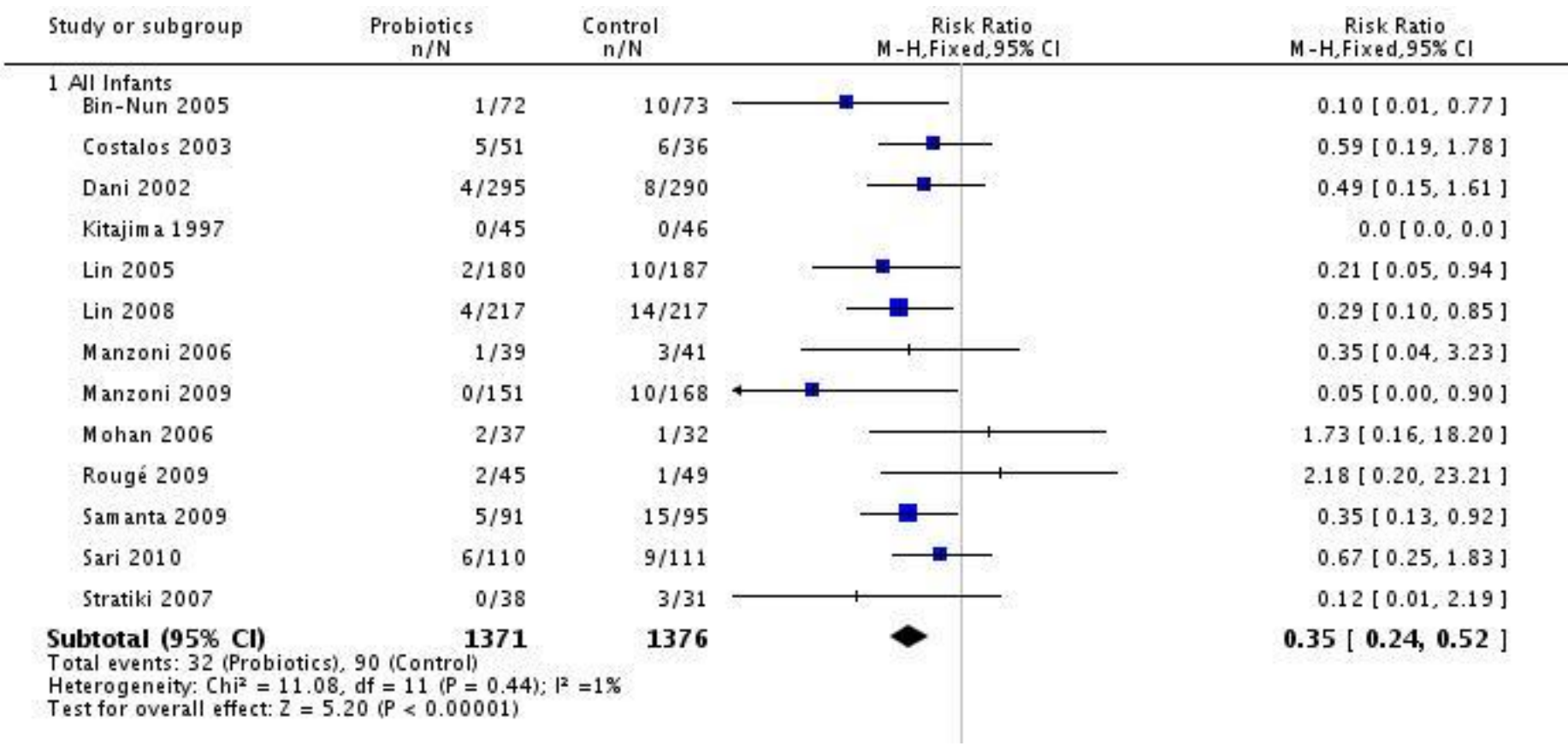
Heterogeneity: Tau² = 630.48; Chi² = 1169.13, df = 34 (P < 0.00001); I² = 97%
Test for overall effect: Z = 5.48 (P < 0.00001)

Mean Difference IV, Random, 95% CI

-100 -50 0 50 100
Favours experimental Favours control

**Duration of diarrhoea (hours):** 35 trials / 4555 infants/children
Allen et al; Cochrane Database of Systematic Reviews 2010

# Prevention of NEC in preterm infants




**Risk of NEC:** 16 trials / 2842 infants

AlFaleh et al. *Cochrane Database of Systematic Reviews* 2011

# Prebiotics

Srinivasjois 2009: oligosaccharide supplementation of formula in neonates ≤37 weeks. 4 RCTs / 126 infants:

- –preventing NEC and sepsis - not reported
- –improve growth - not reported
- –stool characteristics - not reported
- –gut colonisation – increase in bifidobacterial counts (2 trials)

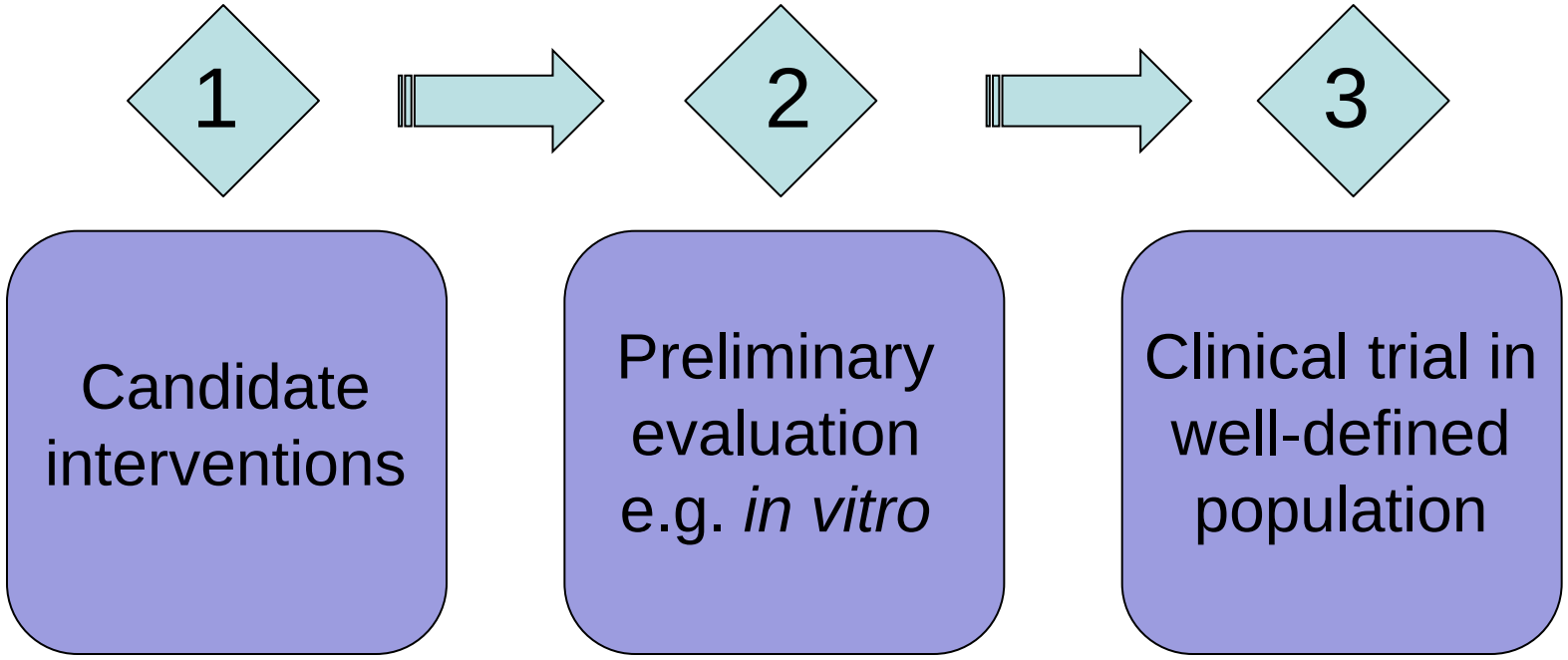
Osborn 2007**:** Prebiotics in infants for prevention of allergic disease and food hypersensitivity. 5 studies.

*Insufficient evidence*

# Probiotics – research in to practice

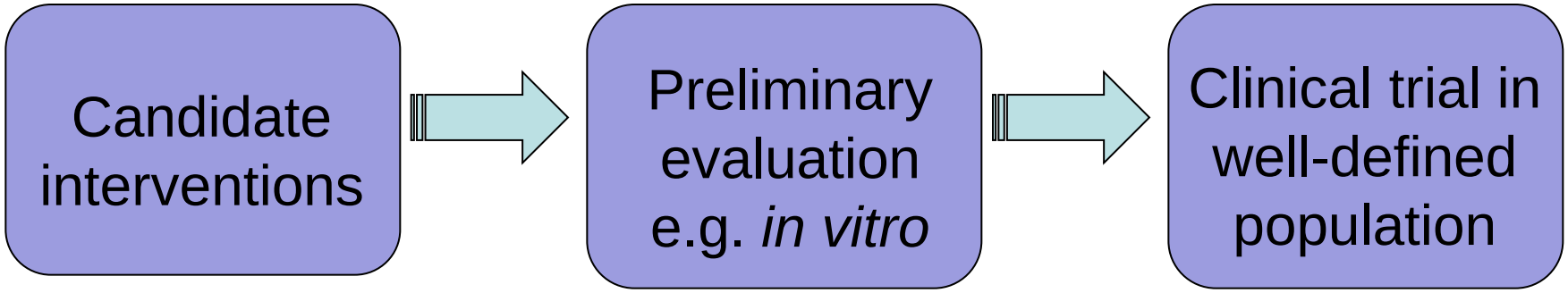
- Proof of principle confirmed for some diseases
- Why no clinical practice guidelines?

# Investigational model




*How does this work for pre- or probiotics?*

# Investigational model




*Very large number of candidate probiotics / regimens*
- single strains vs combinations
- synbiotics
- dose (no. organisms)
- timing / duration of administration

Limited *in vitro* models

Mechanisms complex
- nutrition
- anti-pathogen
- mucosal defence
- inflammation
- immunity

Target diseases often heterogeneous / complex
- acute infectious diarrhoea
- antibiotic-associated diarrhoea

# Simple sum …

Too many candidates X Unable to select best candidate

Complex mechanisms X Heterogeneous clinical population = ***Too difficult!!***

# Closing the research-practice gap

- Develop more / better *in vitro* models, but …
- Practical approach:
  - Select candidates with “best evidence”
  - Well characterised, quality-controlled pre- / probiotics
  - Large trials of clearly defined populations – definitive results

***Design trials so that they contribute to meta-analysis!***

# Obstacles

- Where evidence is good, is a placebo group now acceptable?
- Monitor safety - especially
  - in “new” environments (e.g. preterm infants)
  - post-marketing in sub-groups
- FAO / EU FSA restrictions on health claims for “functional foods”

# Thanks for listening!