Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial

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Summary

**Background** Antibiotic-associated diarrhoea (AAD) occurs most frequently in older (>65 years) inpatients exposed to broad-spectrum antibiotics. When caused by *Clostridium difficile*, AAD can result in life-threatening illness. Although underlying disease mechanisms are not well understood, microbial preparations have been assessed in the prevention of AAD. However, studies have been mostly small single-centre trials with varying quality, providing insufficient data to reliably assess effectiveness. We aimed to do a pragmatic efficacy trial in older inpatients who would be representative of those admitted to National Health Service (NHS) and similar secondary care institutions and to recruit a sufficient number of patients to generate a definitive result.

**Methods** We did a multicentre, randomised, double-blind, placebo-controlled, pragmatic, efficacy trial of inpatients aged 65 years and older and exposed to one or more oral or parenteral antibiotics. A computer-generated randomisation scheme was used to allocate participants (in a 1:1 ratio) to receive either a multistrain preparation of lactobacilli and bifidobacteria, with a total of 6 x 10ⁱ⁰ organisms, one per day for 21 days, or an identical placebo. Patients, study staff, and specimen and data analysts were masked to assignment. The primary outcomes were occurrence of AAD within 8 weeks and *C difficile* diarrhoea (CDD) within 12 weeks of recruitment. Analysis was by modified intention-to-treat. This trial is registered, number ISRCTN70017204.

**Findings** Of 17 420 patients screened, 1493 were randomly assigned to the microbial preparation group and 1488 to the placebo group. 1470 and 1471, respectively, were included in the analyses of the primary endpoints. AAD occurred in 159 (10·8%) participants in the microbial preparation group and 153 (10·4%) participants in the placebo group (relative risk [RR] 1·04; 95% CI 0·84–1·28; p=0·71). CDD was an uncommon cause of AAD and occurred in 12 (0·8%) participants in the microbial preparation group and 17 (1·2%) participants in the placebo group (RR 0·71; 95% CI 0·34–1·28; p=0·35). 578 (19·7%) participants had one or more serious adverse event; the frequency of serious adverse events was much the same in the two study groups and none was attributed to participation in the trial.

**Interpretation** We identified no evidence that a multistrain preparation of lactobacilli and bifidobacteria was effective in prevention of AAD or CDD. An improved understanding of the pathophysiology of AAD is needed to guide future studies.

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Introduction

Antibiotic-associated diarrhoea (AAD) occurs most frequently in older (>65 years) inpatients exposed to broad-spectrum antibiotics, the risk increases progressively with longer treatment courses, and it can occur up to 12 weeks after antibiotic exposure.1 The frequency of diarrhoea varies according to the antibiotic used, occurring in 2–20% of patients given cephalosporins, fluoroquinolones, macrolides, or tetracycline, 5–10% given ampicillin, and 10–25% given co-amoxiclav.1 Additional recognised risk factors for AAD include prolonged hospital stay, treatment with proton pump inhibitors, use of a nasogastric tube, previous hospital admission, and previous gastrointestinal surgery.12

The main mechanism by which antibiotics cause diarrhoea is thought to be through impaired resistance to pathogens as a result of disruption of the gut microbial flora and subsequent changes in the metabolism of carbohydrates, short-chain fatty acids, and bile acids.13 AAD is usually a mild and self-limiting illness but 15–39% of cases are caused by *Clostridium difficile*, which can result in pseudomembranous colitis, toxic megacolon, and high case-fatality.4 Although some investigations have failed to identify high-risk antibiotics,4 cefepime, ceftriaxone, clindamycin, and more recently quinolones have been associated with *C difficile* diarrhoea (CDD).5 Additionally, cumulative antibiotic exposure increases risk.6 Of great concern
since 2003 has been an increased frequency and severity of CDD associated with emergence of the hyper-virulent 027 strain. This concern has led to concerted efforts to prevent infection through improved environmental hygiene, handwashing, antibiotic stewardship, and isolation of patients with diarrhoea. In view of the proposed underlying disease mechanisms, several trials have assessed microbial preparations that might prevent or ameliorate AAD through anti-pathogen effects, such as secretion of bacteriocins, competition for nutrients and binding sites, and enhancement of the immunological barrier function and integrity of the gut mucosa. Meta-analyses have provided some evidence for the efficacy of microbial preparations in prevention of AAD. However, substantial statistical heterogeneity in pooled results, attributable to variation in individual study results, undermined the findings.

Our hypothesis was that the administration of a microbial preparation would reduce the frequency of AAD and CDD in an at-risk population. We aimed to do a pragmatic efficacy trial in older inpatients who would be representative of those admitted to National Health Service (NHS) and similar secondary care institutions and to recruit a sufficient number of patients to generate a definitive result. On the basis of previous evidence, we selected a high-dose, multi-strain preparation of lactobacilli and bifidobacteria, the genera most frequently assessed in clinical trials. In this report, we have used the term microbial preparation and avoided probiotic, on the basis that the effect of the intervention on prevention of AAD was unknown.

Methods
Study design and participants
We did a multicentre, randomised, double-blind, placebo-controlled, two-group trial and have reported the trial protocol previously. Inpatients aged 65 years or older and exposed to one or more oral or intravenous antibiotics in the preceding 7 days, or about to start antibiotic treatment, were recruited by research nurses from medical and surgical wards of three hospitals in south Wales (Abertawe Bro Morganwg University Health Board; ABMUHB) and two hospitals in northeast England (County Durham and Darlington Foundation Trust; appendix p 1). Exclusion criteria were existing diarrhoea, immunocompromised sufficiently to need isolation or barrier nursing, illness needing high dependency or intensive care, prosthetic heart valve, CDD in the previous 3 months, inflammatory bowel disease that had needed specific treatment in the previous 12 months, suspected acute pancreatitis (abdominal pain with serum amylase or lipase more than three times the institutional upper limit of normal), known abnormality or disease of mesenteric vessels or coeliac axis, jejunal tube in situ or receiving jejunal feeds, previous adverse reaction to microbial preparations, and unwillingness to discontinue existing use of probiotics. In practice, patients who were nil by mouth or severely ill and not expected to survive for the period of follow-up were also not invited to join the study.

Patients provided signed informed consent or, when assessed to be unable to do so, signed assent was provided by relatives or carers. The Research Ethics Committee for Wales approved the study on Nov 27, 2008 (No 08/MRE09/18).

Randomisation and masking
Eligible patients were allocated sequentially by research nurses in a 1:1 ratio to the two groups (placebo or microbial preparation) of the study, according to a computer-generated random sequence, stratified by centre and using blocks of variable size. The allocation sequence was generated by the independent statistician and not available to any member of the research team until databases had been completed and locked. Patients, study staff, and specimen and data analysts were masked to assignment. In view of the established safety record of lactobacilli and bifidobacteria there was no provision for emergency unmasking of participants and copies of the allocation sequence were not held at the recruiting centres.

Procedures
The microbial preparation was a lyophilised powder in a vegetarian capsule containing $6 \times 10^{10}$ live bacteria: two strains of *Lactobacillus acidophilus* (CUL60, National Collection of Industrial, Food and Marine Bacteria [NCIMB] 30157; and CUL121, NCIMB 30156) and two strains of *Bifidobacterium bifidum* (Bifidobacterium bifidum CUL20, NCIMB 30153; and *Blactis* CUL34, NCIMB 30172). Identical placebo capsules contained inert maltodextrin powder. The dose was one capsule per day for 21 days with food and, when possible, between antibiotic doses. Unused capsules were collected opportunistically from some participants at the point of use for quantitative bacterial culture by an independent laboratory.

Research nurses collected baseline demographic data, characteristics of patients, and details of antibiotic therapy. Participants were followed up by research staff daily during hospital admission and weekly by phone call after discharge. We had intended that follow-up would continue for 8 weeks after stopping antibiotics. In practice, prolonged follow-up for participants on long courses of antibiotics was not feasible and follow-up was discontinued at 8 weeks after recruitment. Changes to antibiotic treatment, the occurrence of diarrhoea, gastrointestinal symptoms, adverse events, and compliance with the trial interventions were recorded on standard forms.

We defined diarrhoea as three or more loose stools (consistency 5–7 on the Bristol Stool Form Scale) in a 24 h period or as stools described as looser than normal in participants unable to use the scale. Stool samples...
were collected only during episodes of diarrhoea and were analysed for *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, *Escherichia coli* O157, and ova, cysts, and parasites in a wet film according to routine laboratory practice. Detection of viruses was done according to the clinical context and during suspected diarrhoea outbreaks. In ABMUHB, detection of *C. difficile* toxins was by an in-house tissue culture assay with confirmation by enzyme immunoassay (Premier Toxins A&B; Meridian Bioscience, Cincinnati, OH, USA). In the two hospitals in northeast England, the VIDAS *Clostridium difficile* A & B assay (bioMérieux SA, Marcy l’Etoile, France) was used until June 2010, when detection of glutamate dehydrogenase (*C. DIFF QUIK CHEK; TECHLAB, Blacksburg, VA, USA) was used in conjunction with the toxin assay. Hospital laboratory records were reviewed for occurrence of diarrhoeal stools positive for *C. difficile* toxins until 12 weeks after recruitment.

### Statistical analysis

The primary outcomes were the occurrence of AAD within 8 weeks and CDD within 12 weeks of recruitment. AAD was diarrhoea occurring in association with antibiotic therapy and without detection of diarrhoeal pathogens or an alternative explanation (eg, laxative treatment). Patients with AAD and a positive stool *C. difficile* toxin assay were diagnosed as CDD.

Secondary outcomes were severity and duration of AAD and CDD, abdominal symptoms, serious adverse events, duration of hospital stay, the acceptability of the microbial preparation, and quality of life. CDD was managed by the patient's clinical team and severity of the episode classified according to UK national guidelines from information collected from case records. Quality of life was assessed by the generic 12-item short form survey (SF12 v2), which was administered by research nurses at baseline, and 4 and 8 weeks. Additionally, we

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**Figure 1:** Trial profile

*Identity of trial intervention unknown because of an error in labelling at one hospital site. † Second enrolment in study excluded because of possible carry-over effects from first enrolment in study.
Baseline characteristics of participants by treatment group

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Microbial preparation (n=1470)</th>
<th>Placebo (n=1471)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton</td>
<td>102/1470 (6.9%)</td>
<td>101/1471 (6.9%)</td>
</tr>
<tr>
<td>Morriston</td>
<td>742/1470 (50.5%)</td>
<td>737/1471 (50.1%)</td>
</tr>
<tr>
<td>Bhindend</td>
<td>94/1470 (6.4%)</td>
<td>97/1471 (6.6%)</td>
</tr>
<tr>
<td>Durham</td>
<td>269/1470 (18.3%)</td>
<td>278/1471 (18.9%)</td>
</tr>
<tr>
<td>Darlington</td>
<td>263/1470 (17.9%)</td>
<td>258/1471 (17.5%)</td>
</tr>
</tbody>
</table>

Admitted from
- Home: 1345/1469 (91.6%) vs 1344/1468 (90.9%)
- Residential care: 58/1469 (3.9%) vs 67/1468 (4.6%)
- Other hospital: 37/1469 (2.5%) vs 39/1468 (2.7%)
- Other: 29/1469 (2.0%) vs 28/1468 (1.9%)
- Cigarette smoker: 140/1470 (9.5%) vs 120/1471 (8.2%)
- Drinks alcohol: 459/1470 (31.2%) vs 482/1471 (32.8%)

Comorbid illnesses
- Hypertension: 779/1455 (53.5%) vs 812/1457 (55.7%)
- COPD: 350/1459 (24.0%) vs 354/1462 (24.2%)
- Diabetes: 357/1465 (24.4%) vs 314/1468 (21.4%)
- Asthma: 237/1462 (16.2%) vs 232/1465 (15.8%)
- Renal disease*: 122/1455 (8.7%) vs 139/1461 (9.5%)
- Dementia or Alzheimer’s disease: 61/1449 (4.2%) vs 80/1459 (5.5%)
- Other: 97/1452 (6.7%) vs 100/1458 (6.9%)

Previous gastrointestinal surgery: 203/1448 (14.0%) vs 212/1449 (14.6%)
- Nasogastric tube in situ: 5/1469 (0.3%) vs 2/1464 (0.1%)
- Hospital admission in past 8 weeks: 488/1470 (33.2%) vs 448/1471 (30.5%)
- Live bacteria consumed in past 2 weeks*: 72/1470 (4.9%) vs 45/1471 (3.1%)

Data are n/N (%) or median (IQR). COPD=chronic obstructive pulmonary disease. *Established by case note review by the patient’s physicians when necessary. 1Self-reported consumption of live bacteria, probiotics, or live yoghurt.
allocated (figure 1). The main reason for non-recruitment was participants who declined to take part (9068, 52·1%), mainly because of unwillingness to take an additional medication.

Baseline characteristics were generally much the same in the 1470 participants assessed in the microbial preparation group and the 1471 in the placebo group (table 1). Indications for antibiotic treatment were much the same in the two study groups, with the most common indication being respiratory, thoracic, and mediastinal disorders (appendix p 2). Exposure to antibiotics was similar in the two groups (table 2). Median number of days between hospital admission and starting an antibiotic was 0 (IQR 0–1) in both groups (p=0·35). Non-antibiotic drug treatment was common starting an antibiotic was 0 (IQR 0–1) in both groups (appendix p 3).

In all participants during the 3 weeks when taking the trial interventions, abdominal symptoms and other morbidity were much the same in the study groups, compared with the placebo group. Additional clinical signs, laboratory variables, and severity classification in patients with CDD were also similar in the two groups (appendix p 5). During the period of follow-up, no patient with CDD was identified as having pseudomembranous colitis, needed colectomy, had a recurrence, or died from the illness.

Post-hoc analysis identified that most episodes of AAD (195/266, 73·3%) and CDD (22/29, 75·9%) occurred within 4 weeks of recruitment. Diarrhoea attributable to causes other than AAD occurred in seven (0·5%) participants overall with a similar frequency in both intervention groups (appendix p 5).

Duration of hospital stay; morbidity were much the same in the two study groups (relative risk [RR] 1·04; 95% CI 0·84–1·28; p=0·71; odds ratio [OR] is about the same; table 3). Per-protocol analysis showed much the same result (data not shown). In participants with AAD, stool samples were obtained for testing from 93 of 159 (58·5%) in the microbial preparation group and 88 of 153 (57·5%) in the placebo group. CDD was an uncommon cause of AAD and occurred in 0·99% (29) of participants with a similar frequency in each group (RR 0·71; 95% CI 0·34–1·47; p=0·35; OR is about the same; table 3).

Covariate analysis identified that the occurrence of AAD was predicted by duration of antibiotic treatment, antacid therapy, and duration of hospital stay; CDD was predicted by duration of antibiotic treatment. The adjusted treatment effect of the intervention on occurrence of AAD and CDD was much the same as the unadjusted effect (appendix p 3).

In all participants during the 3 weeks when taking the trial interventions, abdominal symptoms and other morbidity were much the same in the study groups, except for small but statistically significant differences in the frequency of flatus and having a nasogastric tube in situ (table 3). Morbidity was also similar in the two study groups throughout the whole period of follow-up (data not shown). Median duration of hospital admission was similar in the microbial preparation (n=1452; 4 days, IQR 1–11) and placebo groups (1447; 4 days, 1–11; p=0·87; figure 2).

Duration and severity of AAD and CDD and frequency of associated symptoms was much the same in the two intervention groups (appendix p 4) except that in CDD bloating was more common in the microbial preparation compared with the placebo group. Additional clinical signs, laboratory variables, and severity classification in patients with CDD were also similar in the two groups (appendix p 5). During the period of follow-up, no patient with CDD was identified as having pseudomembranous colitis, needed colectomy, had a recurrence, or died from the illness.
participants in the microbial preparation group and ten (0.7%) patients in the placebo group (RR 0.70; 95% CI 0.27–1.84). In the microbial preparation group, six patients had norovirus diarrhoea and one was diagnosed with non-specific colitis. In the placebo group, six patients had norovirus diarrhoea, one had diarrhoea after taking laxatives, two had drunk a large volume of fruit juice, and one had abnormal clotting and melaena.

Compliance with the trial interventions was known for 1462 participants in the microbial preparation and 1465 in the placebo group and was much the same in both study groups (figure 3). 777 (53.1%) participants in the microbial preparation group and 766 (52.3%) in the placebo group were observed or reported as taking all 21 doses. The corresponding figures for 14 or more doses were 1104 (75.5%) and 1106 (75.5%). Accounting for compliance in covariate analysis did not materially alter the risk of AAD (OR 1.02; 95% CI 0.80–1.30) or CDD (0.66; 0.30–1.47). 34 unused microbial preparation capsules collected at the point of use all contained at least $1.62 \times 10^{10}$ viable bacteria and 33 placebo capsules tested were sterile.

578 (19.7%) participants had one or more serious adverse event; the frequency of serious adverse events was much the same in the two study groups (appendix pp 6–10). The most common events were respiratory, thoracic, and mediastinal disorders (83 of 1470 [5.6%] vs 87 of 1471 [5.9%]); gastrointestinal disorders (44 [3.0%] vs 35 [2.4%]); and cardiac disorders (42 [2.9%] vs 28 [1.9%]) in the microbial preparation and placebo groups, respectively. No serious adverse event was attributed to participation in the trial.

SF-12 v2 mental component summary, physical component summary, and subscale scores were similar at baseline and, with the exception of vitality, tended to increase either by 4 or 8 weeks. Changes from baseline were much the same in each group (appendix p 11).

**Discussion**

Administration of a high dose preparation of lactobacilli and bifidobacterium did not show the effect of prevention of AAD in our trial of nearly 3000 older inpatients. Analysis of secondary outcomes including diarrhoea severity, frequency of abdominal symptoms, length of hospital stay, and quality of life showed no evidence of a beneficial effect attributable to the microbial preparation. Accounting for potential risk factors for AAD and compliance with the trial interventions did not significantly change the findings. Per-protocol analysis produced consistent results with the intention-to-treat analysis.

As far as we are aware, our pragmatic study done in busy NHS hospitals is the largest trial so far for this problem (panel, figure 4). By contrast with many previous trials, we confirmed the viability of the microbes at the point of use. Our study had several weaknesses. Although we attempted to minimise the exclusion criteria...
Panel: Research in context

Systematic review

Several meta-analyses of trials of microbial preparations in the prevention of AAD have suggested a beneficial effect including the most comprehensive review so far (63 trials; 11,811 participants), which reported that microbial preparations reduced the risk of AAD (random effects analysis: RR 0.58; 95% CI 0.50–0.68). However, as in other reviews, the clinical trials included varied substantially in participant characteristics, the microbial preparations tested, antibiotic exposure, and trial settings, and the reliability of this pooled result was undermined by large statistical heterogeneity (I²=54%). Subgroup analyses accounting for these factors did not explain the heterogeneity. As in a Cochrane review of microbial preparations in the prevention of AAD in children, trial design and reporting were often poor.

For the prevention of CDD, efficacy of the microbial preparation in our study was consistent with the findings of a meta-analyses (20 trials, 3,818 people; random effects model: RR 0.58; 95% CI 0.50–0.68). Although there was consistency in results across studies, this meta-analysis included trials of many different microbes, including the yeast Saccharomyces boulardii, included both children and adults, and research methods and reporting were assessed to be poor in many studies. For both AAD and CDD, the variability in trials precludes the development of clinical guidelines.

In an attempt to reduce clinical heterogeneity, we restricted our search to randomised controlled trials that assessed lactobacilli and bifidobacteria in older inpatients exposed to antibiotics. We searched Medline, the Cochrane Library of Systematic Reviews, CENTRAL and DARE from date of inception to April 2013, and Embase (from 1996 to April 2013) using the search terms “antibiotic-associated diarrhoea”, “probiotic”, “Lactobacillus”, “Bifidobacterium”, and “elderly” and also hand-searched the references from previous systematic reviews.

For AAD, we identified only four trials that either studied older patients or the participants recruited had an average age of older than 65 years (figure 4). Although the pooled result showed a statistically significant risk reduction in AAD in patients receiving microbial preparations, the difference was small and unlikely to be of clinical significance. Furthermore, despite limiting the scope of the studies, substantial statistical heterogeneity (I²=90%) undermines the reliability of this finding.

For CDD, we identified only one previous trial that has reliably reported outcomes in this age group; CDD was reduced in participants receiving a combination of Lactobacillus casei DN-114 001, L bulgaricus, and Streptococcus thermophilus (none of 56; 0%) compared with those assigned placebo (nine of 53; 17.0%). However, the frequency of CDD in the control group was high (17.0%) and patients were highly selected.

Interpretation

Administration of a high dose preparation of lactobacilli and bifidobacterium did not show the effect of prevention of AAD in our trial of nearly 3000 older inpatients. Overall, we believe that there is insufficient evidence to support the use of any microbial preparation for the prevention of AAD in older inpatients.

**Table:** Meta-analysis of trials of lactobacilli or bifidobacteria, or both, in the prevention of antibiotic-associated diarrhoea in older inpatients

<table>
<thead>
<tr>
<th>Microbial preparation</th>
<th>Placebo</th>
<th>Risk difference (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al, 2013</td>
<td>159</td>
<td>1470</td>
<td>0.00 (-0.02 to 0.00)</td>
</tr>
<tr>
<td>Baussuell et al, 2007</td>
<td>44</td>
<td>47</td>
<td>-0.20 (-0.37 to -0.02)</td>
</tr>
<tr>
<td>Berwai et al, 2003</td>
<td>105</td>
<td>97</td>
<td>-0.11 (-0.22 to -0.01)</td>
</tr>
<tr>
<td>Hickson et al, 2007</td>
<td>57</td>
<td>56</td>
<td>-0.22 (-0.37 to -0.07)</td>
</tr>
<tr>
<td>Stockenhuber et al, 2008</td>
<td>340</td>
<td>338</td>
<td>-0.14 (-0.18 to -0.09)</td>
</tr>
<tr>
<td>Total</td>
<td>203</td>
<td>274</td>
<td>-0.04 (-0.06 to -0.02)</td>
</tr>
</tbody>
</table>

Heterogeneity χ²=40.39, df=4, p=0.0001, I²=90%
Test for overall effect Z=3.58, p=0.0003

**Figure 4:** Meta-analysis of trials of lactobacilli or bifidobacteria, or both, in the prevention of antibiotic-associated diarrhoea in older inpatients

*From Mantel-Haenszel fixed effects analysis.

to patients clearly predisposed to diarrhoea and those who might be at specific risk from bacterial supplements, we recruited fewer than one in five eligible patients. The main reason for non-participation was the unwillingness of people already receiving medicines to take an additional preparation. This practical difficulty needs to be considered when developing novel interventions for older patients with many comorbidities. Ethnic diversity was low in our study but was representative of the local older populations. Despite the low conversion rate, we recruited from a range of medical and surgical wards in five hospitals and the baseline characteristics, comorbidity, and indications for antibiotic treatment suggest that our findings are relevant to older inpatients in NHS and similar secondary care settings.

Our trial suggests that properties common to many so-called probiotic bacteria, such as the production of lactic acid, are not effective against AAD in older inpatients.
The design of further intervention studies is hampered by a poor understanding of the pathophysiology of AAD. Potentially important but largely unknown factors include the mechanisms by which specific antibiotics cause diarrhoea and how these mechanisms might be affected by characteristics of the pretreatment enteric flora, which varies between individuals and is affected by age, chronic disease, frailty, diet, residence, and care setting. Also, whether specific strains of microbes possess specific anti-diarrhoeal mechanisms needs further investigation.

Many episodes of AAD were of short duration and we failed to obtain stool samples for testing in about 40% of participants with diarrhoea. When reported, this issue has also been a problem in smaller trials with shorter follow-up. Although these missing samples probably resulted in some missed cases of CDD in our study, the low frequency of CDD (0–99% overall) is consistent with falling rates in England, Wales, and other settings associated with other approaches to prevention of AAD.

The proportion of stools tested in our study was much the same in the two groups and, in view of the absence of efficacy of the microbial preparation against AAD, it seems unlikely that the missing stool analyses have biased the estimate of intervention effect against CDD. Overall, further assessment of novel interventions for the prevention of CDD needs to take account of its falling frequency in some settings so that potential benefits are balanced with potential risks and cost.

Our findings do not provide statistical evidence to support recommendations for the routine use of balanced with potential risks and cost.

Our findings do not provide statistical evidence to support recommendations for the routine use of balanced with potential risks and cost.

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