

The economic case for prevention of population vitamin D deficiency

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1 **The economic case for prevention of population vitamin D**
2 **deficiency: a modelling study using data from England and Wales**

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25 **Abstract**

26

27 **Background:** Vitamin D deficiency (VDD) affects the health and wellbeing of millions
28 worldwide. In high latitude countries such as the United Kingdom (UK), severe complications
29 disproportionately affect ethnic minority groups.

30 **Objective:** To develop a decision-analytic model to estimate the cost-effectiveness of
31 population strategies to prevent VDD.

32 **Methods:** An individual-level simulation model was used to compare: (I) wheat flour
33 fortification; (II) supplementation of at-risk groups; and (III) combined flour fortification and
34 supplementation; with (IV) a 'no additional intervention' scenario, reflecting the current
35 Vitamin D policy in the UK. We simulated the whole population over 90 years. Data from
36 national nutrition surveys were used to estimate the risk of deficiency under the alternative
37 scenarios. Costs incurred by the health care sector, the government, local authorities, and the
38 general public were considered. Results were expressed as total cost and effect of each
39 strategy, and as the cost per 'prevented case of VDD' and the 'cost per Quality Adjusted Life
40 Year (QALY)'.

41 **Results:** Wheat flour fortification was cost-saving as its costs were more than offset by the
42 cost-savings from preventing VDD. The combination of supplementation and fortification
43 was cost-effective (£9.5 per QALY gained). The model estimated that wheat flour
44 fortification alone would result in 25% fewer cases of VDD, while the combined strategy
45 would reduce the number of cases by a further 8%.

46 **Conclusion:** There is a strong economic case for fortifying wheat flour with Vitamin D, alone
47 or in combination with targeted vitamin D3 supplementation.

48

49 **Introduction**

50 Vitamin D helps to maintain adequate levels of calcium and phosphorus in the body, playing a
51 fundamental role in bone and muscle health (1). The main source of Vitamin D is sunlight
52 exposure and many behavioural, cultural or environmental factors increase the risk of VDD
53 by limiting the skin's direct exposure to sunlight. Risk factors for VDD include, for example,
54 sun screen use, air pollution, indoors lifestyles, full body clothing, and living in high latitude
55 settings (2,3). People with dark pigmented skin who live in setting with limited sunlight, such
56 as high latitude countries are also at a higher risk for VDD, as well as older adults,
57 particularly if institutionalised. VDD can lead to poor health and its symptoms manifest as
58 osteomalacia, bone pain, muscle weakness and consequent increased risk of falls. In children,
59 severe VDD additionally causes hypocalcaemia (low levels of calcium in the blood), which is
60 associated with seizures, tetany and heart failure (4,5), and rickets with osteomalacic leg
61 bowing, muscle weakness and delayed infant development. Morbidity from VDD is
62 predominantly found in individuals from Black and Asian Minority Ethnic (BAME) groups
63 living in high-latitude countries, including in the UK (6,7), the US (8), Canada (9),
64 Scandinavian countries (10–13) and Australia (8,14). Nonetheless, VDD is common in many
65 populations across the world, regardless of ethnicity.

66 In response, most countries have adopted policies to increase the populations' intake of
67 vitamin D, which generally consist of a combination of supplementation and food fortification
68 strategies (15). In the UK, multivitamin supplements containing vitamin D are recommended
69 to all infants and children up to the age of four, as well as to pregnant women and
70 breastfeeding mothers (16). These vitamins are provided free-of-charge to those in low-
71 income households. In addition, infant formulas and spreadable fats are mandatorily fortified,
72 while other foods including breakfast cereals and milk substitutes are voluntarily fortified.
73 While both supplements and fortified foods are important sources of vitamin D for the UK

74 population, evidence suggests supplementation policies are not working (7,17) and the mean
75 daily vitamin D intake is still below the Reference Nutritional Intake (RNI) of 400 IU per day
76 (2,18). Therefore, rickets and hypocalcemic complications remain a serious health issue and
77 cause of death in infants, particularly in the BAME group (4,7,19,20). Evidence shows that
78 vitamin D status, which is measured through the blood concentration of a Vitamin D
79 metabolite, the 25-hydroxyvitamin D [25(OH)D], is suboptimal in 13% of the European
80 population (21). In the UK population, 20% of adults and 16% of children aged between 11
81 and 18 years are estimated to be VDD (2), with the BAME group being, by far, the most
82 affected (10,12,22–25).

83 So far, the economic evidence needed to inform and underpin VDD prevention policies has
84 been limited (26). To the best of the authors' knowledge', there is no evidence on the cost-
85 effectiveness of preventing population VDD through food fortification or a combination of
86 food fortification and supplementation, even though the latter is the approach taken in most
87 countries (15). This study estimates the cost-effectiveness of preventing VDD using the
88 population of England and Wales as a simulated cohort and compares the strategies of
89 supplementation of at-risk groups, wheat flour fortification, and a combination of the two
90 approaches.

91

92 **Methods**

93 An individual-level state-transition model was developed to compare four different strategies
94 to prevent population VDD. A state transition model was chosen to allow recurrence of VDD
95 over the life course, and individual-level simulation was used to make the most efficient use
96 of available data on risk heterogeneity for VDD in the population, as well as to account for
97 individual pathways across the model's time horizon (27,28). The model used a one-year
98 cycle length, and both costs and benefits were discounted at 3.5% per year, as recommended

99 by the UK National Institute for Health and Care Excellence (NICE) (29). The base case
100 analysis was done from a societal perspective and results reported using incremental cost
101 effectiveness ratios (ICER) in the form of cost per additional quality-adjusted life year
102 (QALY) gained, and cost per prevented case of VDD. The model was built in TreeAge Pro
103 2016 software, and followed modelling (28,30) and reporting (31) guidelines for good
104 practice.

105 The model comprised three main health states (**Figure 1**). These health states were mutually
106 exclusive and represent clinically relevant stages:

107 1) Vitamin D deficient (VDD): all children with serum 25(OH)D concentrations below
108 30nmol/L (3) and adults with serum 25(OH)D below 50 nmol/L (32).

109 2) Vitamin D sufficient (VDS): all children with serum 25(OH)D concentrations above
110 30nmol/L (3) and adults with serum 25(OH)D above 50 nmol/L (32).

111 3) Dead: based on all-cause mortality and naturally treated as an absorbing state.

112

113 **[Figure 1]**

114

115 The majority of the VDD population were assumed to be asymptomatic. Within the model,
116 asymptomatic individuals followed a pathway with the possibility of remaining deficient or
117 becoming sufficient over time. For the deficient population who become symptomatic,
118 children were assigned a risk of developing rickets and hypocalcemic complications, and
119 adults a risk of developing osteomalacia. Younger adults aged between 19-64 years old who
120 acquire osteomalacia suffer from diffuse pain and muscle weakness. Older adults with
121 osteomalacia had a modest increased risk of falls due to pain and muscle weakness. The full
122 model structure depicting the clinical pathways for children and adults with symptomatic
123 VDD can be found in the supplementary material (Figure S1 and Figure S2).

124 The starting cohort within the model was simulated based on the population of England and
125 Wales, according to its age, sex and ethnicity distributions (33). The following four
126 alternative strategies were compared: (I) wheat flour fortification at 400IU of Vitamin D per
127 100 g of wheat flour; (II) free supplementation to all at-risk groups; (III) a combination of
128 flour fortification and supplementation; and (IV) no additional intervention, i.e. maintaining
129 the current fortification and supplementation policy of providing supplements to young
130 children, pregnant women and breastfeeding mothers within low-income households, and
131 fortifying certain food groups. Wheat flour was chosen as the most appropriate food for
132 fortification since, contrary to milk and spreadable fats, flour is a staple food across multiple
133 ethnic groups, including Asian, African, Caribbean, and white ethnic groups, and therefore
134 will potentially reach multiple at-risk groups. Evidence from Scandinavian countries shows
135 that milk supplementation is not as effective in reaching ethnic minority groups as it is in
136 reaching white ethnic groups (15). Regarding safety, a UK study that compared vitamin D
137 fortification of milk, flour and a combination of both showed that flour fortification alone
138 presented the lowest risk of toxicity in the population (34). Wheat flour is already fortified in
139 the UK, and addition of vitamin D to the mix of added nutrients is likely to carry lower
140 implementation barriers than targeting an industry that has no fortification infrastructure, in
141 place, such as milk in the UK. The baseline risk of VDD was estimated using individual-level
142 intake data reported from the National Diet and Nutrition Survey (NDNS) (18,35). The intake
143 of vitamin D included all food sources (natural and fortified foods, including voluntarily
144 fortified). Differences in intake by age group and sex were considered.

145 The effectiveness of wheat flour fortification in reducing the risk of being VDD by sex was
146 derived from Allen et al.'s nutrition model (34,36). Ethnicity specific effects were not
147 available and therefore the same effect was assumed for white and BAME populations. The

148 full list of the transition probabilities used in the model for the current UK policy and wheat
149 flour fortification is presented in the supplementary material (Table S1.A. and Table S1.B.).
150 The effect of the supplementation programme was based on data provided by a local
151 government organization in London, UK (37), which recorded the uptake of free vitamin D
152 supplements using an electronic card system. In this Local Authority, all children up to 4
153 years old, pregnant women and breastfeeding mothers were eligible to receive free Vitamin D
154 supplements. In our model, supplements were provided to all sub-populations at risk of
155 symptomatic VDD including all infants and young children up to 18 years old; individuals of
156 all ages from BAME backgrounds; and all individuals aged over 65 years. In the absence of
157 data on the uptake of supplements by adults and older children (>4 years old), we assumed the
158 same uptakes in older and younger children to that of children <4 years, and the adult uptake
159 to be the same as that of pregnant and breastfeeding women. The model assumed a
160 supplement dosage of 400IU per day for all groups except for the elderly, who received
161 800IU per day as per the recommended minimum dose to prevent falls (38). The effectiveness
162 of the combined scenario (wheat flour fortification plus supplementation of at-risk groups)
163 was estimated as the additive effectiveness of each strategy alone.

164 **Outcomes**

165 Preventing VDD in the population reduces the risk of poor bone and muscle health. The
166 outcome unit used for the cost-effectiveness analysis was the number of cases of VDD
167 prevented. For the cost-utility analysis, the health-related quality of life (HRQoL) for a given
168 health state was combined with the time spent in that health state to formulate QALYs. The
169 preference-based quality of life values (i.e. utilities) applied to estimate QALYs were sourced
170 from two HRQoL studies, published elsewhere (39), one focusing on VDD in children, and
171 the other in adults (supplementary material, table S2).

172

173 Costs

174 Cost data were derived from multiple sources (supplementary material, table S3). For the
175 wheat flour fortification strategy, the price of dried vitamin D was obtained from a UK
176 commercial flour supplier of the food industry (LFI (UK) Ltd). The costs of re-labelling
177 packages, used in a sensitivity analysis, and the public sector costs of enforcing mandatory
178 fortification were sourced from the Food Standards Agency's study of wheat flour
179 fortification with folic acid (40). The cost structure of the supplementation programme was
180 based on the Local Authority's supplementation programme (37), which was pharmacy-led. It
181 was assumed that supplements would be supplied through community pharmacies, which
182 would receive an initial financial incentive for participating in the programme and
183 reimbursements for the cost of the supplements dispensed. An additional incentive would be
184 provided for each supplement dispensed to encourage sustained adherence to the programme.

185 Uncertainty and sensitivity analyses

186 Several sensitivity analyses were conducted to determine how sensitive the model results
187 were to the assumptions made (Table 1). First, the time horizon was varied to 5 and 10 years.
188 Second, the discount rate for both costs and benefits was set to 1.5%. Third, the perspective
189 was altered to include only public sector costs, therefore eliminating all private costs borne by
190 the food industry. Fourth, following the Food Standards Agency report on the cost of
191 fortifying flour with folic acid in the UK (40), the model included a conservative estimate for
192 the food industry costs of relabelling flour packages, and all products containing flour, such as
193 cakes and biscuits. Fifth, the model assumed no disutility from asymptomatic VDD. Sixth, the
194 starting cohort was altered to include a higher proportion of BAME individuals, reflecting the
195 population mix of many large UK cities (33). Finally, a probabilistic sensitivity analysis was
196 conducted based on 10,000 iterations of a Monte Carlo simulation, using the model parameter

197 distributions listed in the supplementary material (Tables S4-S11). All analyses was
198 conducted in TreeAge Pro 2017, R1.

199

200 [Table 1]

201

202 **Results**

203 The model base case analysis showed that wheat flour fortification was cost-saving, which
204 means that it led to fewer costs and more benefits when compared to the current national
205 policy in England and Wales, and is therefore described as dominant (Table 2). All other
206 strategies were found to be superior to the current national policy in terms of cases of VDD
207 prevented.

208 The model estimated that if the current VDD policy is kept in place, there will be almost 40
209 million new cases of VDD – asymptomatic and symptomatic - over the next 90 years.
210 Introducing wheat flour fortification would result in a 25% reduction in this number, and if
211 that is combined with an additional supplementation programme then a further 8% would be
212 prevented (33% in total). The model estimated that wheat flour fortification would lead to an
213 increased expenditure of £0.12 per person per year based on consumption estimates that
214 include common flour based products such as cakes and biscuits (41). The model found the
215 strategy of flour fortification to be cost-saving, saving approximately £65 million over a 90-
216 year time horizon. If food fortification is combined with supplementation, then this would
217 lead to an additional cost of nearly £2 per case of VDD prevented but more cases of VDD
218 would be prevented when compared to fortification alone.

219

220 [Table 2]

221

222 The analysis showed that wheat flour fortification at 400IU per 100g of flour combined with
223 targeted supplementation at 400IU for children up to 18 years old and all individuals from
224 BAME backgrounds and 800IU for all individuals older than 65 years old is cost-effective.
225 The intervention costs on average £0.38 per person across the whole population (total costs
226 over the 90 years modelled is 250 million) and leads to an average gain of 0.04 QALYs,
227 resulting in an ICER of £9.50 per QALY gained (table 3). Under commonly applied UK
228 thresholds of willingness to pay per QALY, this represents a highly cost-effective use of
229 resources.

230 **[Table 3]**

231
232 The sensitivity analyses showed the model results were not sensitive to the majority of the
233 assumptions made. Consistently, with each subsequent sensitivity analysis, the model showed
234 the flour fortification strategy to be dominant and the combined strategy to impose a small
235 cost but to be highly cost-effective. Evidence from the literature suggests that asymptomatic
236 VDD – (serum concentrations of 25(OH)D levels below the deficiency threshold, but no overt
237 symptoms), if coexisting with limited dietary calcium, are regarded as a pre-clinical health
238 risk state, with diffuse pain (1), muscle weakness and fatigue (42), and thus likely to impact
239 on quality of life. In the base case analysis, a detrimental impact on HRQoL was assumed
240 based on an expert elicitation study (39). We tested this assumption in a sensitivity analysis
241 and noted that when it is assumed that the asymptomatic VDD health state results in the same
242 quality of life as being vitamin D sufficient, then the combined strategy has no additional
243 benefit (supplementation material, appendix 4).
244 Finally, the probabilistic sensitivity analysis (**Figure 2**) showed that for willingness to pay
245 values of up to £200 per QALY, wheat flour fortification is the recommended option. For

246 values above £200 per QALY, a combination of wheat flour fortification and supplementation
247 of all-at risk groups is the optimal strategy.

248

249 **[Figure 2]**

250

251

252 **Discussion**

253 Our model found that implementing strategies to prevent VDD is likely to be cost-effective
254 and wheat flour fortification to be cost-saving as compared to the current policy in England
255 and Wales. The costs of implementing and running the fortification scheme were more than
256 compensated for by the health care savings from preventing more cases of VDD.
257 Alternatively, the combined strategy of adding Vitamin D to wheat flour and extending the
258 coverage of supplementation to all at-risk groups would be highly cost-effective strategy.
259 Therefore, for an additional cost, the combined strategy prevents more cases of VDD when
260 compared to fortification alone and under conventional decision-making rules(43), this
261 additional cost would be regarded as a highly cost-effective use of public resources.

262

263 These results of our study are in line with published economic evaluations of food
264 fortification programmes for other micronutrients, such as folic acid (44–46), which have
265 found food fortification to be cost-saving, in pre- and post-implementation studies. The
266 economic advantage of food fortification lies in the wide-coverage and shared costs across the
267 private sector, consumers and the government. Food fortification has the potential to target
268 hard-to-reach populations, overcoming some of the problems with low uptake of
269 supplementation programmes. Moreover, fortification has a far lower burden on the health
270 care budget than supplementation alternatives, as most costs of the food fortification

271 programme are borne by the food industry, and passed on to the consumer. However, a
272 combined strategy offers both a nutritional safety net to the population by fortifying the food
273 chain, and a targeted supplementation scheme to those who are most in need.

274

275 We have included children, BAME groups and individuals aged over 65 years old in the at-
276 risk group of the population. Even though most severe cases of VDD have been reported in
277 BAME mothers and their new-borns, overall pregnant women benefit from adequate levels of
278 25OHD. Most vitamin D supplementation policies around the world already target pregnant
279 women and infants. When considering new public health approaches to reach at-risk and
280 vulnerable groups, pregnant women should continue to be a target group for the strategy of
281 supplementation.

282

283 The analysis presented here is based on hypothetical scenarios with conservative assumptions
284 applied to increase confidence in the results. For example, potential savings in primary care
285 associated with consultation of general practitioners and testing were not included, such as the
286 economic burden from routine 25(OH)D testing. In children alone, these costs were estimated
287 to be £1.7 million (at 2014 prices) (47). As new and more expensive diagnostic tests are
288 introduced, the economic burden is likely to increase. Furthermore, conservative estimates
289 regarding the modelling of VDD-related falls in the elderly were also applied, based on a
290 recent economic evaluation study by Poole et al (2015) (48).

291

292 We have focused on the benefits of vitamin D to bone and muscle health. The emerging
293 evidence of potential wider benefits of maintaining a healthy vitamin D status such as
294 prevention of cancer and cardiovascular disease (49,50), acute respiratory infections, (51) and
295 other illnesses (52), suggests that the impact of public health measures to tackle vitamin D

296 deficiency might be even stronger than that reported in this study. A recent meta-analysis
297 using individual patient data from over 10,000 individuals found that vitamin D supplements
298 reduced the risk of acute respiratory infections, such as colds and the flu, which have a
299 tremendous burden in population health and health systems (51). As more robust evidence on
300 non-musculoskeletal effects of vitamin D from interventional studies become available, there
301 is potential for future models to incorporate these additional benefits. If the same public
302 health measures compared in our model are able to prevent other diseases, the cost-
303 effectiveness results will be even more favourable than the ones we present here.

304 One of the strengths of the model is that it was informed by direct communication with
305 stakeholders, including clinical experts, local UK public health organisations, established
306 researchers with experience in economic evaluation of micronutrient interventions, and expert
307 investigators in the economics of food fortification. Moreover, this is the first model to
308 compare supplementation and food fortification with vitamin D independently, as well as the
309 combination of both in the same analysis, which is a more meaningful way of representing the
310 relevant alternatives for policy makers to consider. Our findings were robust when tested
311 under a number of deterministic sensitivity analyses and a probabilistic sensitivity analysis.

312

313 The model has some limitations. Data on the costs and uptake of the supplementation
314 programme were sourced from a Local Authority, and were extrapolated to a nation-wide
315 scenario. Regarding the costs, for example, purchases at the national level might achieve
316 economies of scale and result in lower costs. To account for this uncertainty, each relevant
317 model input (eg. cost estimates) was assigned a wide distribution within the probabilistic
318 sensitivity analysis. There was a lack of data on the uptake of supplements by ethnic groups
319 who have different risk profiles for developing VDD. In the absence of uptake data by ethnic
320 group, equivalent levels were applied to all ethnic groups. Furthermore, the cost and

321 effectiveness of the combined strategy was assumed to be the sum of the costs and
322 effectiveness of the flour fortification and supplementation strategies combined. In reality, if
323 implemented simultaneously, interactions between the two strategies are likely, although it is
324 unknown in which direction. Finally, the model only included the health-related benefits from
325 preventing VDD and any other benefits beyond health were not included. Economic
326 evaluation requires that the relevant benefits and costs of each of the policy alternatives are
327 quantifiable. This is the greatest challenge when applying standard economic evaluation
328 methods to the prevention of micronutrient deficiencies. The benefits from reducing the
329 prevalence of vitamin and mineral deficiencies are wide but hard to measure (53). Nutrition,
330 including vitamin D status, impacts human development from conception until the later stages
331 of life (54–56). Moreover, poor nutrition affects socioeconomically disadvantaged groups of
332 the population, and tackling it would have a wider economic benefit by addressing health and
333 social inequalities (57). For example, there would be a clear social benefit from reducing the
334 prevalence of VDD in minority ethnic groups, as it would reduce any stigma associated with
335 rickets in children (58).

336

337 The effectiveness of any fortification programme depends on a number of programme design
338 choices, for example, the food chosen needs to be consumed by the targeted population, and
339 the price increase of the final product should be kept low, so that no access barriers based on
340 income are not created (53,59). These features of a programme are particularly important in
341 the context of VDD since BAME groups are at a higher risk. Other studies have highlighted
342 that there is a need to collect data on the diet and nutritional status of BAME populations in
343 the UK (60). We corroborate such needs. To date, nutritional data from the NDNS have not
344 been reported by ethnic group. Doing so would facilitate implementation of food fortification
345 programmes, the effectiveness of which could be monitored using the existing structures, as

346 done in other countries such as Finland (21). Fortifying flour would ensure that population
347 serum 25(OH)D concentrations are raised to safe levels with supplementation used to target
348 subgroups that the fortification programme may not reach effectively.

349

350 VDD is wide-spread in the population, it has a negative impact on HRQoL with a burden of
351 disease that is much larger than rickets and osteomalacia. VDD and its complications are
352 preventable and well-planned public health strategies can be highly cost-effective and even
353 cost-saving. Biological, environmental, cultural, historical, and economic factors influence
354 how VDD affects the population, as well as the cost and effectiveness of alternative strategies.
355 Therefore, tackling population VDD in England and Wales requires efforts from
356 multidisciplinary professionals, such as clinicians, nutritionists, health economists, public
357 health professionals, and policy makers.

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368 **Conflict of interest**

369 None declared

370 **Author Contributions**

371 All authors contributed to designing the research. MA conducted the research and analyzed
372 data supervised by LA, MP, WH and EF. All authors contributed substantially to writing the
373 paper, while MA and EF had primary responsibility for final content. All authors have read
374 and approved the final manuscript.

375

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Figures legends

Figure 1 – Illustration of the model structure

Figure 2 – Cost-effectiveness acceptability curve (CEAC) showing the probability of alternatives to prevent VDD being cost-effective at increasing acceptability thresholds