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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Examining the Cost-Effectiveness of Moving the Healthy Start Vitamin Programme from a Targeted To a Universal Offering

## Final Report

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All confidential data are redacted

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# Executive Summary

## 1. INTRODUCTION

In 2012, the Annual Report of the Chief Medical Officer ("Our children deserve better – Prevention pays") highlighted the importance of vitamin supplementation in mothers and young children and the growing concerns about vitamin D deficiency. Infants and children under age 5 and pregnant and breastfeeding women are advised to take a daily supplement of vitamin D. However, national surveys indicate that uptake of vitamin D supplements is low, particularly among low income groups.

Healthy Start is a UK-wide, means tested, statutory scheme which aims to provide a nutritional safety net for low-income pregnant women, new mothers and for children under the age of 4 years. Those in receipt of qualifying income-related benefits or tax credits are eligible to receive the vitamin supplements. Pregnant women under the age of 18 are also eligible for the scheme, regardless of whether or not they receive benefits. Healthy Start children's vitamin supplements contain the amount recommended by the COMA committee (1) of vitamins A, C and D for children aged six months to four years. Women's vitamins contain the recommended amount of folic acid, vitamin C and vitamin D for pregnant and breastfeeding women.

Uptake of Healthy Start vitamin supplements is very low (some studies suggest that less than 10% redeem their vitamin vouchers (2, 3). Key barriers to uptake include practical difficulties with obtaining supplies of the vitamins, their short shelf-life (of the children's vitamins), the complex ordering and reimbursement system, complicated assessment of eligibility and difficulties in identifying a convenient and accessible location through which they could be distributed. Making the scheme universally available may overcome some of these issues. The National Institute for Health and Care Excellence (NICE) recently released guidance on increasing vitamin D supplement use among at risk groups (4).

In response to a recommendation from the Chief Medical Officer, the Department of Health asked the National Institute for Health and Care Excellence (NICE) to examine the cost effectiveness of moving the Healthy Start vitamin programme from the current targeted offering, to a universal offering. Therefore, NICE has commissioned this research to investigate the differential cost-effectiveness between offering the scheme on the current targeted, versus a universal, basis. This report describes the economic model developed to answer this question and the results of this economic evaluation.

## 2. OBJECTIVES

To develop an economic model to inform answers to the following questions:

"Would it be cost-effective to move the Healthy Start Vitamin Programme from the current targeted offering to a universal offering, according to the following two scenarios:

**a.** Within the current parameters of the scheme (all pregnant women from 10 weeks; women with a child under 12 months; and children over 6 months and under 4 years);

**b.** All women planning a pregnancy; pregnant women; women with a child aged under 12 months; infants aged from 0 to 6 months and children aged from 6 months to 5 years."

Subsidiary questions were as follows:

1. "Is universal provision of Healthy Start supplements to women seeking to become pregnant cost-effective, compared with no provision under Healthy Start?"
2. "Is universal provision of Healthy Start vitamin supplements to women who are less than 10 weeks pregnant cost-effective, compared with no provision under Healthy Start?"
3. "Is universal provision of Healthy Start supplements for infants aged 0 to 6 months cost-effective, compared with no provision under Healthy Start?"
4. "Is universal provision of Healthy Start supplements for children aged 4 to 5 years cost-effective, compared with no provision under Healthy Start?"
5. "Would universal provision of supplements create a 'spill over' effect by increasing uptake in the current target group and would this be cost-effective compared with the current targeted offering?"
6. "What is the incremental cost-effectiveness ratio of extending the eligibility for universally available vitamins to:
    - **i.** Infants from birth to 6 months compared with providing them for those aged over 6 months;
    - **ii.** Children between their fourth and fifth birthday compared with providing them until their fourth birthday;
    - **iii.** Women less than 10 weeks pregnant compared with providing them to those over 10 weeks pregnant (the current target);
    - **iv.** Women intending to become pregnant?"

## 3. RESULTS

The model results focus on two scenarios. In scenario 1, the current Healthy Start offering is extended to a universal offering for all the subgroups that currently receive the Healthy Start supplements (Objective A). In scenario 2, the current Healthy Start offering is extended universally as in Scenario 1 and also to the extended subgroups (as defined in Objective B).

The model estimates that where the universal offering is extended within the current subgroups (scenario 1), the scheme would not be considered cost-effective with an incremental cost-effectiveness ratio (ICER) of £620,898. The model estimates that a universal scheme in scenario 2 is likely to be cost-effective, with an ICER of £6,528. In scenario 2, the scheme is likely to be considered cost-effective for any subgroup combinations that includes 'women planning a pregnancy and before 10 weeks pregnant'. The cost-effectiveness results are driven by the quality adjusted life year (QALY) gains from reducing neural tube defect (NTD) pregnancies through the provision of folic acid.

However, it is important to note that these model results must be tempered by great uncertainties in the model, all of which reduce the reliability of any conclusions which may be drawn.

## 4. DISCUSSION

There is a lot of uncertainty in the economic model, which impacts upon the reliability of the conclusions. Many of the model inputs are uncertain due to a lack of data on the uptake of vitamin supplements, intervention and treatment costs and utilities and a lack of experience of how a universal scheme would be implemented.

It is also important to note that the model assigns QALYs only to pregnancies affected by a NTD, which are reduced through the provision of folic acid. QALYs are not assigned to any health benefits from supplementation with vitamins A, C or D. This does not mean that there are no quality of life benefits, only that the data are not available to accurately populate the model.

The scheme appears cost-effective where it is extended to women planning a pregnancy and before 10 weeks pregnant. Within the model it has been assumed that Healthy Start vitamin supplements will be distributed to this subgroup in the same manner as other subgroups already included in the scheme. Should targeting these women prove more costly than assumed, extension of the scheme will be less cost-effective.

The model report includes many sensitivity and scenario analyses to account for the uncertainty in the model. It is not possible to say with certainty whether or not moving the Healthy Start scheme from a targeted scheme to universal provision would be cost-effective. However, the model results suggest that moving to a universal scheme could be cost-effective for some subgroup combinations, specifically when women planning a pregnancy and before 10 weeks pregnant is included.

# Acknowledgements

The authors would like to thank the NICE Expert Reference Group for their input in the model development phase. We are extremely grateful to Eleanor McGee, Tricia Morris (Department of Health) and Gwenda Scott for their contribution to the model inputs. Finally, the authors would also like to thank the Healthy Start project leads and all those who provided data for consideration for the model.

# Abbreviations and Glossary

## ABBREVIATIONS

| | |
|---|---|
| BMEG | Black and Minority Ethnic Groups |
| BSA | Business Services Authority |
| CPH | Centre for Public Health |
| DH | Department of Health |
| DNSIYC | Diet and Nutrition Survey of Infants and Young Children |
| ERG | Expert Reference Group |
| ICER | Incremental cost-effectiveness ratio |
| IFS | Infant Feeding Survey |
| LIDNS | Low Income Diet and Nutrition Survey |
| LRNI | Lower reference nutrient intake |
| NDNS | National Diet and Nutrition Survey |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NTD | Neural tube defect |
| QALY | Quality-adjusted life year |
| QOL | Quality of life |
| WHO | World Health Organisation |
| YHEC | York Health Economics Consortium |

## GLOSSARY

| | |
|---|---|
| Incremental cost-effectiveness ratio (ICER): | The difference in mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest[1]. |
| Folate: | Folate intake encompasses naturally occurring folates in foods plus synthetic folic acid added to fortified foods and supplements. |
| Folic acid: | Folic acid is a water-soluble vitamin belonging to the B-complex group of vitamins. |
| Lower Reference Nutrient Intake (LRNI): | The adequacy of vitamin or mineral intake can be expressed as the proportion of individuals with intakes below the LRNI. The LRNI for a vitamin or mineral is set at the level of intake considered likely to be sufficient to meet the needs of only 2.5% of the population[2]. |
| Quality-adjusted life year (QALY): | A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. |

[1] From NICE glossary https://www.nice.org.uk/glossary?letter=q

[2] Definition from NDNS report (2)

| | |
|---|---|
| | QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a zero to one scale). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance[1]. |
| Retinol equivalent: | Retinol is the predominant circulating form of vitamin A in the blood[3]. Retinol equivalent is a unit used for quantifying the vitamin A value of sources of vitamin A. The risk of being below the Vitamin A lower reference nutrient intake used within the model is based upon retinol equivalents. Intakes are expressed as retinol equivalents to take account of the lower biological efficiency of carotenoids compared to retinol. |
| Symptomatic vitamin D deficiency: | For the purposes of this report, symptomatic vitamin D deficiency is defined as a combination of clinical findings such as bow legs, rickety rosary, tetany, convulsions due to hypocalcaemia, radiological evidence, biochemistry results such as raised alkaline phosphatase (ALP) with or without high parathyroid hormone levels, or low levels (<25 nmol/l) of 25- hydroxycholecalciferol (25OHC) (Zipitis *et al.,* 2006). This definition is based on the definition in the two papers from which effectiveness and cost data were obtained (5, 6). |
| Tornado diagrams: | A method of presenting multiple univariate sensitivity analyses on one graph. Tornado diagrams allow the reviewer to assess which of the model's parameters have the greatest influence on the model's results. |
| Univariate sensitivity analysis: | Also known as 'one-way sensitivity analysis'. It allows a reviewer to assess the impact that changes in a certain parameter will have on the model's results. This is the simplest form of sensitivity analysis since only one parameter is changed at one time. |

[3] From WHO report http://www.who.int/vmnis/indicators/retinol.pdf

# Section 1: Background

The National Institute for Health and Care Excellence (NICE) Centre for Public Health (CPH) commissioned York Health Economics Consortium (YHEC) to carry out a systematic cost-effectiveness review and to develop an economic model. The purpose of the cost-effectiveness review was to assess the available evidence of the cost-effectiveness of supplementation with the vitamins contained within the Healthy Start vitamin supplements. The aim of the cost-effectiveness modelling is outlined in more detail below. The development of both the cost-effectiveness review and the cost-effectiveness modelling was supported by input from the Expert Reference Group (ERG).

Healthy Start is a UK-wide, means tested, statutory scheme which aims to provide a nutritional safety net for low-income pregnant women, new mothers and for children under the age of 4 years. Those in receipt of qualifying income-related benefits or tax credits are eligible to receive the vitamin supplements. Pregnant women under the age of 18 are also eligible for the scheme, regardless of whether or not they receive benefits. Healthy Start beneficiaries receive vouchers that can be spent on milk, fruit and vegetables and formula. They also receive vitamin coupons for women's tablets or children's vitamin drops (7). The current project focuses only on the vitamin component of the Healthy Start scheme.

The aim of the cost-effectiveness modelling element of the current project was to develop a *de novo* economic model to examine the cost-effectiveness of moving the Healthy Start vitamin programme from the current targeted offering to a universal offering. The purpose of this exercise was not to determine whether supplementation with Healthy Start vitamin supplements as currently offered is cost-effective, but to estimate the differential cost-effectiveness between offering the scheme on the current targeted, versus a universal, basis. The specific questions were:

"Would it be cost-effective to move the Healthy Start Vitamin Programme from the current targeted offering to a universal offering, according to the following two scenarios:

**a.** Within the current parameters of the scheme (all pregnant women from 10 weeks; women with a child under 12 months; and children over 6 months and under 4 years);

**b.** All women planning a pregnancy; pregnant women; women with a child aged under 12 months; infants aged from 0 to 6 months and children aged from 6 months to 5 years."

Subsidiary questions are as follows:

1. "Is universal provision of Healthy Start supplements to women seeking to become pregnant cost-effective, compared with no provision under Healthy Start?"
2. "Is universal provision of Healthy Start supplements to women who are less than 10 weeks pregnant cost-effective, compared with no provision under Healthy Start?"
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    - **iii.** Women less than 10 weeks pregnant compared with providing them to those over 10 weeks pregnant (the current target);
    - **iv.** Women intending to become pregnant?"

The following sections report on the model structure which has been developed with input from the ERG. The model structure is described in Section 2. The evidence that has been used to populate the model and the areas in which there are gaps in the data or uncertainty in the inputs are outlined in Section 3 and 4. Section 5 reports the model results for the base case values within the model. This section outlines the results for various scenarios in which the universal offer of Healthy Start vitamin supplements is extended to the various different subgroups within the model. This section also reports extensive scenario and sensitivity analysis. Section 6 provides a summary and discussion.

# Section 2: Model Structure

## 2.1 OVERVIEW

The population subgroups that were included in the model are as follows. The model set-up allows the user to select specific population groups:

- Population subgroups included in the current Healthy Start offering:
  - Pregnant women after 10 weeks;
  - Women with a child up to 12 months;
  - Infants and children over 6 months and under 4 years.
- Extended subgroups:
  - Women planning a pregnancy;
  - Pregnant women before 10 weeks;
  - Infants aged 0 to 6 months;
  - Infants and children over 4 years and under 5 years.

The vitamins included in the model were those that are included in the Healthy Start vitamin supplements. The Healthy Start maternal vitamin supplements contain the following within one multivitamin tablet:

- Folic acid;
- Vitamin C;
- Vitamin D.

Whilst, the Healthy Start children's vitamin supplements contain the following:

- Vitamin A;
- Vitamin C;
- Vitamin D.

Table 2.1 shows which vitamin supplements are supplied to each population group. For example, in the subgroup 'pregnant women after 10 weeks' a tick is shown for folic acid, vitamin C and vitamin D as these are included in the Healthy Start maternal vitamin supplements. A cross is shown for vitamin A as this is not included in the Healthy Start maternal vitamin supplement. The extended groups (considered to address the modelling questions) show those subgroups that do not currently receive any supplement provision from Healthy Start vitamin supplements. However, the extended subgroups still have a baseline uptake as some of the people in these subgroups may purchase vitamin supplements privately or get vitamins supplements on prescription. In each table, the baseline level of uptake is the proportion of people taking any vitamin supplement (whether a Healthy Start vitamin supplement or a vitamin supplement from some other source) currently, with the Healthy Start scheme running with targeted provision (whether a Healthy Start vitamin supplement or a vitamin supplement from some other source). The new level

of uptake is the proportion of people taking any vitamin supplement in the scenarios where the Healthy Start scheme is made universal.

**Table 2.1: Population subgroups and vitamins included in the model**

| | Folic acid | Vitamin A | Vitamin C | Vitamin D |
|---|---|---|---|---|
| **Currently targeted groups** | | | | |
| Pregnant women after 10 weeks | ✓ | x | ✓ | ✓ |
| Women with a child up to 12 months | ✓ | x | ✓ | ✓ |
| Infants and children over 6 months and under 4 years | x | ✓ | ✓ | ✓ |
| **Extended groups** | | | | |
| Women planning a pregnancy | ✓ | x | ✓ | ✓ |
| Pregnant women before 10 weeks | ✓ | x | ✓ | ✓ |
| Infants aged 0 to 6 months | x | ✓ | ✓ | ✓ |
| Infants and children over 4 years and under 5 years | x | ✓ | ✓ | ✓ |

The model is structured to allow a range of perspectives to be summarised in the model results. This model takes three perspectives; NHS, public sector (which includes NHS and local authority costs) and societal (which includes public sector costs and costs to individuals). The cost perspective is used to define who a cost is borne by. For example, the cost of Healthy Start vitamin supplements is borne by central government as the Department of Health (DH) pay for the Healthy Start vitamin supplements. Some cost is also borne by local authorities as they use staff time distributing the vitamins. These costs also apply to the public sector which consists of local authority, central government and the NHS. If a societal perspective is taken all of these costs would be included plus the costs to individuals. To give another example, the cost of treating vitamin D deficiency will cost money to the NHS when patients are hospitalised. However, these costs will not apply to local or central government. Currently, local areas that provide universal supplementation are paid for by the local authority.

The following perspectives can be included in the model:

- NHS;
- Public sector (i.e. local authority, central government and NHS);
- Societal.

A public sector perspective has been taken in the base case, rather than local authority and central government perspectives separately as costs are borne by a combination of the three public sector bodies. Attempting to disentangle these costs and any health benefits assigned would involve assumptions being made, rendering the results less meaningful.

Some individuals may already buy supplements but may not do so if the supplements are made universally available, in these cases the costs to the public sector would increase for no additional benefit. This is considered within the relevant perspectives.

## 2.2 OVERVIEW OF MODEL OUTCOMES

Following discussion with the ERG, it was recommended that, where possible, the model outcome measures would focus on:

- Measures of nutrient intake, specifically, the number of people below the lower reference nutrient intake (LRNI);
- Accepted measures of nutritional status (e.g. for vitamin D a plasma concentration of 25 hydroxyvitamin D (25[OH]D, of below 25 nmol/litre);
- Functional measures to which the outcomes could be linked to (for example, neural tube defects for folic acid).

It was agreed that, for vitamins A and C, there were no functional outcomes suitable for inclusion in the economic model. While generally being unwell, having poor immunity or faltering growth may be associated with poor nutritional status; these are not unique to having a poor vitamin A or C status and are difficult to quantify. As such, it is difficult to assign costs and utilities to these health states. Therefore, for these vitamins, the model calculated only the number of people below the LRNI with no specific treatment cost or QALYs assigned to this.

Members of the ERG commented that there are functional outcome measures for vitamin D, such as rickets and ostemalacia, but these conditions are relatively rare. There are some other functional outcomes for vitamin D relating to general health, but as for vitamins A and C, these are currently hard to quantify. Data is available on symptomatic vitamin D deficiency (5, 6) and as costs can be assigned to this, this was selected as the outcome measure for vitamin D. However no quality of life data for this outcome could be identified. For the purposes of this report, symptomatic vitamin D deficiency is defined based on the definition in the two papers from which effectiveness and cost data were obtained (5, 6). It is defined as a combination of clinical findings such as bow legs, rickety rosary, tetany, convulsions due to hypocalcaemia, radiological evidence, biochemistry results such as raised alkaline phosphatase (ALP) with or without high parathyroid hormone levels, or low levels (<25 nmol/l) of 25- hydroxycholecalciferol (25OHC) (6). The ERG also considered hypocalcaemic fits as an independent functional outcome. This discussion is documented in Section 4.3.4. For folic acid the functional outcome of neural tube defect (NTD) pregnancies was included in the model, with costs and QALYs applied.

The following measures were identified to model the number of people below the various nutritional status markers. The information required was the probability of being below each marker for those who take supplements and for those who do not:

- Vitamin A – retinol (below 0.35 umol/l = severe deficiency) (0.35 to 0.70 umol/l = marginal deficiency);
- Vitamin C – plasma vitamin C (below 11 umol/L = deficiency) (11 to 28 umol/lL = depletion);
- Vitamin D – lower than 25 nmol/L = ‘low status’;
- Folate – lower than 10nmol/l (serum) or lower than 340nmol/l (red blood cell folate) = biochemical folate deficiency.

Unfortunately, the information needed to populate the model with the number of supplement takers and non-supplement takers below various nutritional status markers was not identified.

The National Diet and Nutrition Survey (NDNS) reported nutritional status for vitamin C, D and A[4] and the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) reported nutritional status for vitamin D. Although the Low Income Diet and Nutrition survey (LIDNS) reported nutritional status for all four vitamins, this survey did not report results for the general population, as was required by the model. Further, although the NDNS and DNSIYC reported nutritional status, this was not reported separately for those taking supplements and those not taking supplements (which was the information needed to calculate the probability input in the model). The NDNS raw data were analysed but following discussions with the ERG it was concluded that the sample sizes of children providing a valid blood sample when split into supplement taker and non-supplement taker were too small to carry out any meaningful analysis.

This information was not crucial to modelling the cost-effectiveness of moving the Healthy Start scheme from a targeted to a universal offering, although it would have provided valuable additional information.

Table 2.2 summarises which outcome measures were included for each nutrient within the model.

**Table 2.2: Outcome measures used in the economic model**

| Outcome measure | Folic acid | Vitamin A | Vitamin C | Vitamin D |
|---|---|---|---|---|
| Nutrient intake | x[cd] | ✓ | ✓ | x |
| Nutritional status | x[c] | x | x | x |
| Functional outcomes | ✓[a] | x | x | ✓[b] |

[a] Pregnancies affected by a NTD;

[b] Symptomatic vitamin D deficiency;

[c]. As folate;

[d] Folic acid is added to the HS supplements to reduce the risk of NTDs but the dose is far higher than would be required to meet the usual Dietary Reference values for women in the general population who are not planning a pregnancy or in the first trimester of pregnancy. For this reason the ERG decided not to look at the LRNI as an outcome measure for folic acid but to focus on the functional outcome of prevention of NTDs

[4] The NDNS recently released nutritional status results for folate (20 March 2015). However, this was not included in the current report as the data were not in the right format for use in the economic model and due to timing of the release it was not possible to carry out further analyses.

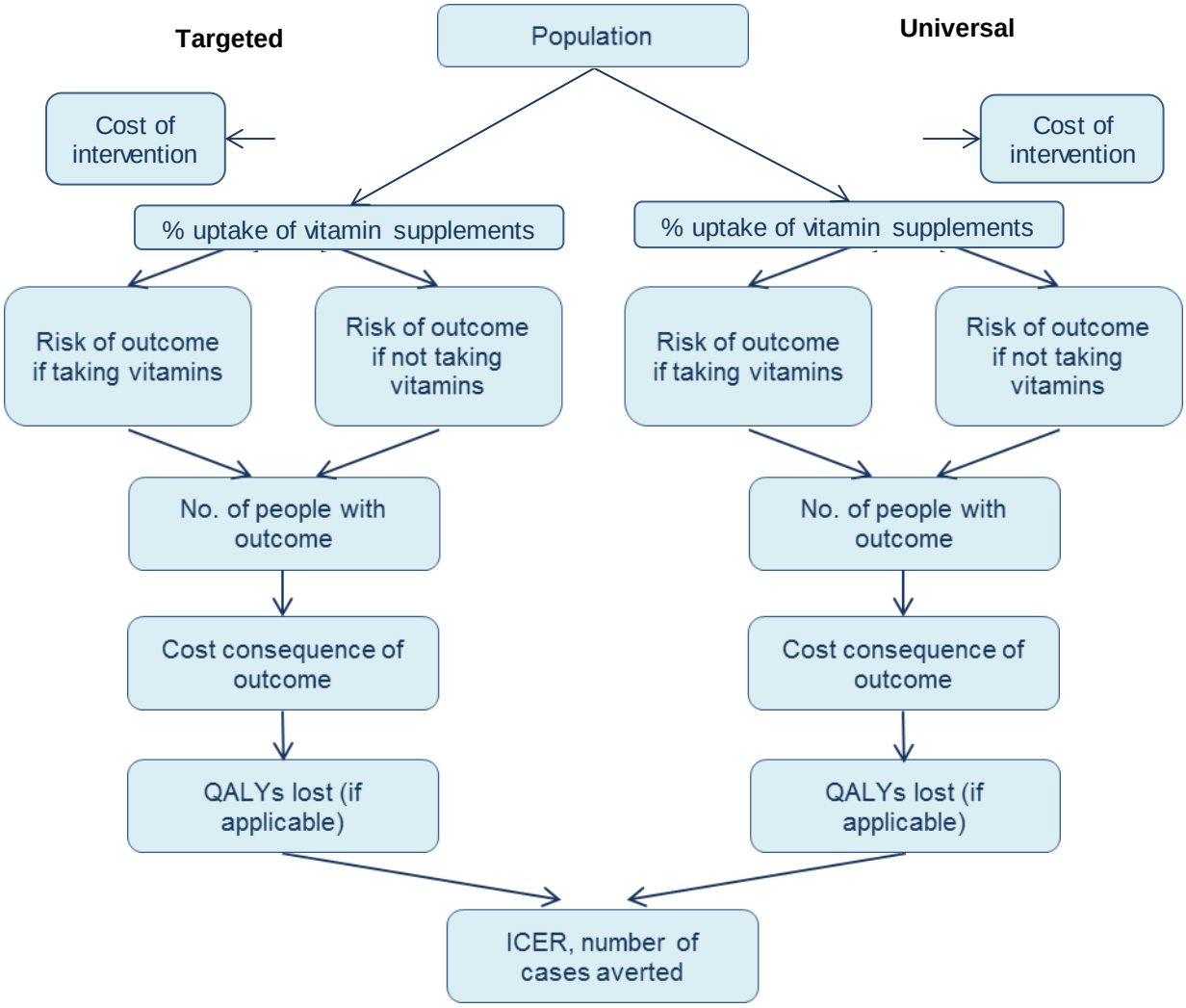
## 2.3 MODEL STRUCTURE

The model structure is outlined in Figure 2.2. This structure has been applied to each vitamin and subgroup included in the model (outlined in Section 2.1). The model structure was based on the estimated number of people taking vitamin supplements in each population group for the targeted and universal approach. Based on the estimated number of people taking vitamin supplements and the probability of each outcome, a weighted average probability for those taking supplements and not taking supplements was calculated. Once the number of people that experience one of the outcomes was calculated, the treatment cost (if applicable) and QALY loss (if applicable) was applied to those people. The cost of the intervention was applied as the cost of the additional supplements for the number of extra people that take Healthy Start vitamin supplements in the universal scenario and any additional set up and running costs of the universal scheme. An incremental cost-effectiveness ratio (ICER) was then calculated. The NICE threshold usually requires the ICER to be below £20,000 to £30,000 for an intervention to be considered cost-effective. Within this report, a cost-effectiveness threshold of £20,000 has been used unless otherwise stated.

As explained in Section 2.2 above, the model did not include the number of people below nutritional status markers for each vitamin by supplement user and non-supplement user as the data have not been identified to populate this. This data is not crucial to the economic modelling; however it would have provided additional information. The structure of the model allows for the inclusion of this information if the data become available in the future.

The number of cases below the LRNI threshold for those vitamins which did not have a defined functional outcome (vitamins A and C) are reported in the model.

**Figure 2.2: Model structure**



# Section 3: Methods and Data Sources

Various data sources have been used to populate the model. Often, the required data were not available and assumptions had to be made. Feedback from the ERG was sought on these assumptions and where assumptions were included the best available data was used. In all cases of substantial uncertainty, extensive sensitivity analyses were undertaken to explore the impact of different assumptions on the model's results.

## 3.1 DATA SOURCES

Several data sources have been used to populate the model. These data sources are referred to throughout the report; therefore, a brief summary of each is provided below. Table 3.1 provides a summary outline of the type of information used from each data source, the way these sources were used in the economic model is explained in more detail in Section 4.

### 3.1.1 National Surveys

The national surveys that were reviewed for relevant information were the National Diet and Nutrition Survey (NDNS (8)), Infant Feeding Survey, 2010 (IFS (9)), Diet and Nutrition Survey of Infants and Young Children (DNSIYC (10)) and the LIDNS (11).

The NDNS, IFS and DNSIYC were used to populate the model (discussed in Section 4). Although the LIDNS does report similar information to the national surveys that were used to populate the model, such as the nutritional status for all four vitamins, it did not report results for the general population as was required to populate the model. The ERG agreed there were not adequate data to model by income level. However, it is important to note that there may be variation in uptake of supplements by income level.

### 3.1.2 Primary Data Collection

Primary data collection was carried out through a survey commissioned specifically for this research project. The aim of the survey was to identify the number of people that currently pay for their own supplement and to identify the type, quantity and price paid for supplementation that was taken by the population groups of interest. Three surveys were developed, one for each of the following population groups: women planning a pregnancy; pregnant women; and women with children aged 0 to 5 (the questions for this population group asked about the women's use of supplements as well as those they gave to their children).

The survey was an online survey which was developed in consultation with the ERG. It was run between 25/11/14 and 02/12/14 in England. The survey was sent to panels of the general population which were then targeted to the population groups of interest. A copy of

the survey questions are available in Appendix A. Responses were received from 180 women planning a pregnancy, 147 pregnant women and 405 women with children 0 to 5 years.

### 3.1.3 Local Cost Data

In order to obtain information about running the Healthy Start scheme at a local level, a costing template was developed. As part of the cost-effectiveness review for this project a mailing list of 539 Healthy Start leads (provided by the NHS Business Services Authority (BSA) at the request of the DH) were sent an email asking if they would participate in the completion of a costing template. Thirty-eight responses were received about the costing template, all of whom were then sent the blank costing template. This resulted in four partially completed templates from areas offering Healthy Start vitamin supplements on a targeted basis and four partially completed templates being received from areas offering Healthy Start vitamin supplementation on a universal basis.

Due to the partial completeness of the templates received and the large variation in responses it was agreed with NICE and the ERG that taking an average of these values was not appropriate. It was agreed YHEC would work closely with two areas delivering Healthy Start vitamin supplements to determine a cost of running the scheme universally and the uncertainty in this input explored in sensitivity and scenario analyses.

### 3.1.4 Central Cost Data

A telephone conference was held with the DH, NICE and YHEC to determine the central cost to the DH of running the Healthy Start vitamin supplement scheme. The DH estimated that the main cost of running the Healthy Start scheme was distributing the food vouchers and that beyond the price paid to NHS Supply Chain for the vitamins, the cost of supplying the vitamin coupons on top of the food vouchers was negligible.

In order to account for the additional applications in the universal scenario the DH provided an estimate of the cost of each application and the cost of reissuing vitamin coupons for the subsequent provision of coupons after the initial application. These costs are described in the relevant inputs section of the report. It has been assumed in the base case that a universal scheme would continue to require applications to be made and coupons to be used. Sensitivity analysis has been undertaken to determine the impact of varying these costs.

**Table 3.1: Summary of data sources**

| Data source* | Model inputs |
|---|---|
| National surveys | Uptake of supplements, effectiveness data** |
| Costing templates | Local costs of running the HS vitamin scheme |
| YHEC survey | To determine how many people pay privately for their vitamins and the average price paid |
| DH data | Central cost of running the HS vitamin scheme to the DH |

* Please note that some information was submitted from industry and although this was considered it was not suitable for use in the economic model. This was because the information provided was not generalisable or internal market research did not provide as many model inputs as the national survey data.

** Effectiveness inputs in the model were used to calculate how many people had either a pregnancy affected by a NTD, symptomatic vitamin D deficiency or were below the LRNI for vitamin A and C in each subgroup.

# Section 4: Inputs

The following sections report in detail on the approach and inputs used for each vitamin. Assumptions are described in the text. The inputs described in this section of the report are those used in the base case and the effect of varying these inputs has been explored through sensitivity and scenario analyses (reported in Section 5.2).

## 4.1 POPULATION INPUTS

The population inputs in the model provide the number of people in each population subgroup annually. Table 4.1 below provides the population figures and data sources used.

**Table 4.1: Population inputs and source**

| Population with the potential to benefit | Universal | Source |
|---|---|---|
| Pregnant women after 10 weeks | 697,911[a b] | ONS, 2013 (12) |
| Women with a child up to 12 months | 718,015[a] | ONS, 2013 (12) |
| Women with a child up to 12 months, who have had another child within that 12 months | 20,104[a] | Chandra *et al.* (2005) (13) |
| Infants and children over 6 months and under 4 years | 2,389,870 | ONS, 2014 (14) |
| Women planning a pregnancy and become pregnant | 393,472[a] | Welling *et al.* (2013) (15) |
| Pregnant women before 10 weeks and have a baby | 718,015[a] | ONS, 2013 (12) |
| Infants aged 0 to 6 months | 341,410 | ONS, 2014 (14) |
| Infants and children over 4 years and under 5 years | 682,820 | ONS, 2014 (14) |

a The number of births been adjusted (increased) to account for multiple births and includes live births only;

b This figure excludes those who have another child within 12 months of a birth to avoid double counting.

The number of pregnancies and the number of children were calculated from Office for National Statistics (ONS) data (12, 14). The starting point was the number of births and the number of pregnancies was calculated from that. The number of births was adjusted to account for multiple births. The number of women who have had another child within 12 months was reported by a study in the USA which was used to calculate the number of women who had a second child within 12 months. The paper reported that 2.8% of women had a second birth in less than 12 months from the first to second birth (13).

A study in 2013 reported the proportion of unplanned pregnancies as 54.8% in the general population (15). This was used as a basis for calculating the number of women who plan a pregnancy. For women planning pregnancy and women before 10 weeks pregnant, the population taking vitamins was then calculated. This included both those with the potential to benefit from vitamins (i.e. having a live birth) and those who do not become pregnant or those that become pregnant and miscarry. The NHS website (16) reports that 84% of couples trying to conceive naturally will do so within one year. Therefore, the population taking vitamins was higher than the population planning and successfully conceiving

(population = 468,419). In addition, Gindler *et al.* (2001) (17) reported that 9.1% of women with confirmed pregnancies miscarry during early pregnancy (this study was carried out in China) and that supplement use did not differ between the two groups. Therefore, the population of women planning a pregnancy and those pregnant before 10 weeks is higher than just those who are pregnant before 10 weeks and who go on to have a baby (population = 789,895).

## 4.2 UPTAKE INPUTS

This section discusses the inputs used to populate the baseline uptake of vitamin supplements and the new level of uptake of vitamin supplements for each population group.

### 4.2.1 Baseline Uptake Inputs

Table 4.2 shows the inputs and sources used to populate the baseline levels of uptake of vitamin supplements for each population group and vitamin.

**Table 4.2: Baseline uptake inputs and sources**

| | Folic acid (%) | Vitamin A (%) | Vitamin C (%) | Vitamin D (%) |
|---|---|---|---|---|
| **Currently targeted groups[f]** | | | | |
| Pregnant women after 10 weeks | 23.0[a] | | 39.0[a,e] | 42.3[a,e] |
| Women with a child up to 12 months | 36.8[a,e] | | 36.8[a,e] | 36.8[a,e] |
| Infants and children over 6 months and under 4 years | | 7.8[b,c,e] | 8.4[b,c,e] | 7.8[b,c,e] |
| **Extended groups** | | | | |
| Women planning a pregnancy | 37.0[a] | | 23.3[a,d,e] | 23.3[a,d,e] |
| Pregnant women before 10 weeks | 79.0[a] | | 39.0[a,e] | 42.3[a,e] |
| Infants aged 0 to 6 months | | 8.3[a,e] | 8.3[a,e] | 8.3[a,e] |
| Infants and children over 4 years and under 5 years | | 12.0[c,e] | 12.0[c,e] | 11.0[c,e] |

a IFS – Infant Feeding Survey, 2010 (9);
b DNSIYC – Diet and Nutrition Survey of Infants and Young Children, 2011 (10);
c NDNS – National Diet and Nutrition Survey, 2008/09 to 2011/12 (8);
d YHEC survey;
e The input has been calculated based on the YHEC survey data and assumptions (see subsequent sections);
f Assumptions have been made throughout this table that the national survey data apply to the model subgroups.

The ERG discussed using uptake data for women planning a pregnancy from Bestwick *et al.* (2014) (18). A scenario analysis (Section 5.3.9) has been carried out using the Bestwick data which showed that this had a minimal impact on the ICER.

#### 4.2.1.1 Pregnant women after 10 weeks

The source used to populate these inputs was the IFS (9), as shown in Table 4.2. For folic acid, the IFS reported the proportion of mothers taking folic acid later on in pregnancy (after 3 months).

The IFS (9) reported the type of supplements taken during pregnancy for some supplements including folic acid. However, the IFS did not explicitly report use of vitamin C supplements. But the proportion taking Healthy Start vitamin supplements; 'multivitamins and iron'; 'multivitamins only' and the proportion taking 'vitamins, iron and folic acid' were included as the assumption was made that these supplement types included vitamin C. Further, some participants may report taking supplements in more than one category. Therefore, this input in the model may be an over estimate of baseline uptake. The raw data of the IFS were checked to ensure that there was no additional data specifically about vitamin C. No new information was identified.

The IFS reported the uptake of vitamin D and Healthy Start vitamin supplements (which contain vitamin D). The assumption was made that the other supplements ('multivitamins and iron', 'multivitamins only' and 'vitamins, iron and folic acid') also contained vitamin D. The assumption was made that vitamin D supplements contained the required dosage. However, some vitamin D supplements may contain less than the required dosage.

The raw data of the IFS were also checked to ensure that there was no additional detail specifically about vitamin D and again, no new information was identified. Therefore, the input used may be a slight overestimate of the true baseline uptake.

The IFS did not report supplement intake according to whether the supplements were taken earlier or later on in pregnancy. Therefore, for both vitamin C and vitamin D, the same baseline uptake rate has been used for pregnant women before and after 10 weeks.

#### 4.2.1.2 Women with a child up to 12 months

The source used to populate these inputs was the IFS (9), as shown in Table 4.2. The IFS reported the proportion of breastfeeding mothers taking supplementary vitamins or iron from 4 weeks to 10 months postpartum. Although these data were not ideal, given that not all women with a child up to 12 months will breastfeed (those women who do breastfeed may have different supplement taking behaviour compared to those who do not breastfeed), it was judged to be more applicable then using supplementation levels from the general female population.

#### 4.2.1.3 Infants and children over 6 months and under 4 years

The sources used to populate the uptake for infants and children over six months and under four years were from the DNSIYC (10) and the NDNS (8), as shown in Table 4.2. The DNSIYC reported the percentage of infants aged 7 months to 18 months consuming any type of supplement. The NDNS reported the percentage of children aged 1.5 to 3 years consuming supplements. A weighted average of the results from both surveys was calculated.

In the main published reports, the DNSIYC and the NDNS did not state whether vitamin A supplements specifically were taken. Neither do they report which vitamins are included in 'multivitamins' or 'any type of supplement'. Therefore, the assumption was made that 'any type of supplement' and 'multivitamins' contained vitamin A and D. The NDNS also reports

'calcium only or with vitamin D' which was also included in the vitamin D uptake. Therefore, this may overestimate the baseline uptake of vitamin A and D.

Similar assumptions were made with vitamin C although the NDNS also reported participants that consumed vitamin C only.

#### 4.2.1.4 Women planning a pregnancy

The IFS (9) and the YHEC survey were used to estimate the uptake for women planning a pregnancy, as shown in Table 4.2. The IFS reported the proportion of mothers who took folic acid before pregnancy.

The YHEC survey showed that of those women taking folic acid, 63% took it in a multivitamin supplement. The assumption was made that this multivitamin supplement would also contain vitamins C and D.

#### 4.2.1.5 Pregnant women before 10 weeks

For women in the early stages of pregnancy (i.e. before 10 weeks), uptake was estimated using the IFS (9), as shown in Table 4.2. The IFS reported the proportion of mothers who took folic acid during the first three months of pregnancy.

For vitamin C and vitamin D, the same assumptions and inputs were used as those described in Section 4.2.1. This is because the IFS reported information on the use of supplements other than folic acid for pregnant women but not by stage of pregnancy and so the same uptake inputs were applied to pregnant women before and after 10 weeks.

#### 4.2.1.6 Infants aged 0 to 6 months

The IFS (9) was used to obtain the uptake rates for infants aged from birth to six months, as shown in Table 4.2. The IFS reported the proportion of babies aged 4 weeks to 6 months given vitamin drops. The assumption was made that the vitamin drops contain vitamins A, C and D.

#### 4.2.1.7 Infants and children over 4 years and under 5 years

Uptake for infants and children between the ages of four and five were estimated using the NDNS (8), as shown in Table 4.2. The NDNS reported the percentage of participants consuming supplements for children aged 4 to 10 years.

As with the other population subgroups using the NDNS, the NDNS did not specify each vitamin in the main published report and therefore an assumption was applied that multivitamins contain vitamins A, C and D.

### 4.2.2 New Level of Uptake in Universal Scenario

The model allows for varying uptake of the supplements in a universal scenario.

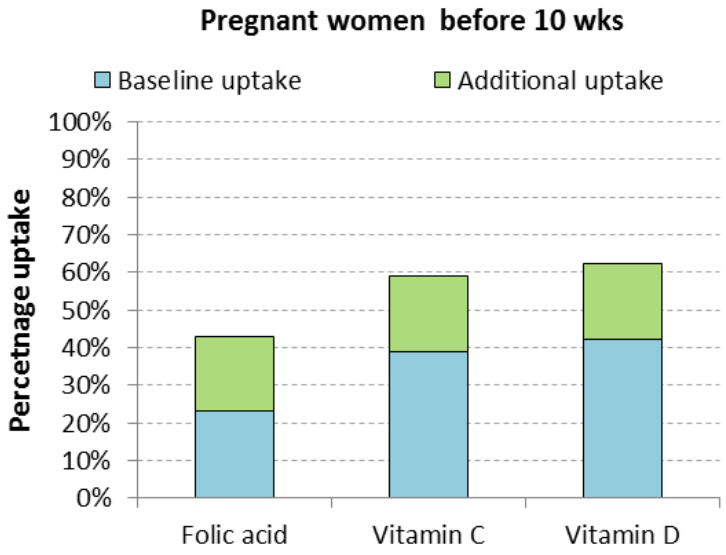
A study carried out in Birmingham, Moy *et al.* (2012) (5) and McGee *et al.* (2013) (19) identified the increase in uptake when Healthy Start vitamin supplements were given universally[5] compared to the targeted offering. The increase in uptake (20 percentage points in women and 17 percentage points in children) observed in these studies was applied to the national survey data to derive the estimated uptake with a universal offering.

The model includes a substitution coefficient that can be used to calculate different uptake scenarios. The substitution coefficient determines how the extra uptake is applied.

The substitution coefficient allows for some of the Healthy Start uptake to replace those that were previously privately purchasing their own supplements.

If the substitution coefficient is 0%, the model assumes that all additional Healthy Start uptake is new uptake (i.e. none of these people were taking supplements before). This is illustrated in Graph 4.1 in which the uptake of Healthy Start vitamins is an additional 20% (the green bar). Because the entire Healthy Start uptake is from people who did not previously take vitamin supplements, the overall uptake has increased by the same amount (20%, the green bar). This is explained in more detail in the technical Appendix B.

**Graph 4.1: Additional uptake with universal offering in the current subgroups (scenario 1)***




* Numbers are illustrative.

[5] The universal scheme in this study consisted of providing vitamins free of charge to pregnant and lactating women and children aged under 5 years.

If the substitution coefficient is 50%, the model assumes that the Healthy Start vitamin supplement uptake is split proportionally between new uptake and substitutes (those that were purchasing privately but have moved to the free Healthy Start vitamin supplements). The proportion depends on the baseline uptake. All other substitution coefficients interpolate between these assumptions. For example, a substitution coefficient of 25% is halfway between 0% and 50% and a substitution coefficient of 75% is halfway between 50% and 100%. The application of the substitution coefficient when baseline uptake is either very low or very high may be more complex. Details of this are provided in Appendix B.

### 4.3 EFFECTIVENESS INPUTS

The effectiveness inputs in the model were used to calculate how many people have either a pregnancy affected by a NTD, symptomatic vitamin D deficiency or are below the LRNI for vitamin A and C in each subgroup.

The number of people in each of the health states described above was calculated using the following method:

$$\begin{aligned} &Number\ of\ people\ that\ have\ an\ outcome \\ &\quad = (number\ of\ people\ taking\ vitamin\ supplements \\ &\quad \times probability\ of\ an\ outcome\ if\ taking\ vitamin\ supplements) \\ &\quad + (number\ of\ people\ not\ taking\ vitamin\ supplements \\ &\quad \times risk\ of\ an\ outcome\ if\ not\ taking\ vitamin\ supplements) \end{aligned}$$

Initially the ERG requested that, for mothers within the first 12 months postpartum, the health outcomes for both the mother and the baby should be included within the model. However, no evidence was identified demonstrating the effect of mothers' supplementation on their babies' nutritional status or health outcomes at the doses provided by Healthy Start. Therefore this could not be included in the model.

The ERG also discussed that the vitamin status of babies in the first month of life may be determined by the mothers' vitamin status during pregnancy. Data were not sought on this issue as an extreme scenario was modelled and the effect on the ICER was negligible[6].

Tables 4.4, 4.5, 4.6 and 4.7 outline the effectiveness inputs and the source of the inputs for folic acid, vitamin A, vitamin C and vitamin D, respectively.

[6] An extreme scenario was modelled in which none those aged 0 to 1 months had vitamin D deficiency and none were provided with Healthy Start supplements in the universal scenario 2. This represents the most extreme scenario in which all mothers take vitamin D supplements and all breastfeed their babies and all of those babies then have sufficient supplementation in the first month. Even with these extreme values, the ICER was reduced by only a small amount (less than £150).

### 4.3.1 Folic Acid

Table 4.4 shows the inputs and sources for the folic acid probability inputs. Recent evidence on the effectiveness of supplementation with folic acid for the prevention of NTDs is lacking. This may be due to the previously established knowledge of the advantages of folic acid supplementation when planning a pregnancy and during the first trimester of pregnancy. The lack of recent data is unlikely to be a major issue, because the dietary supply of folate has only increased slightly in that past three decades. The mean dietary supply of folate as reported in the NDNS in the late 1980s shows only small differences over time as shown in Table 4.3. Further, many studies examine pregnancies affected by a NTD in people who have previously had a pregnancy affected by a NTD (reoccurrence). This may be due to the relatively low prevalence of first occurrence NTDs, meaning that very large sample sizes are needed to produce meaningful results.

**Table 4.3: Mean intake of folate (from food sources only)**

| Age group | Mean 1980s intake µg/d[a] | Mean 2008-2012 intake µg/d[b] |
|---|---|---|
| 16-24 | 198 | 189 |
| 25-34 | 206 | 218 |
| 35-49 | 220 | 225 |

[a] Dietary and Nutritional Survey of British Adults 1986/87

[b] NDNS (8)

A Cochrane review on the effect of periconceptional folic acid supplementation (20) identified only one trial conducted in 1994 (Czeizel *et al.*) examining the first occurrence of a pregnancy affected by a NTD. However, the identified study did not report folic acid supplementation effectiveness in all of the groups required for the model (those planning a pregnancy *and* during pregnancy and during pregnancy only compared to no supplementation). The study (20) did not report on the effectiveness of folic acid supplementation during pregnancy alone.

One study was identified that included the probability of NTDs for the groups needed in the model (Milunsky *et al.,* 1989 (21)). Although this study is not a recent study, it was the only one identified that included the effectiveness data needed to model extending provision to the subgroups defined in Section 2.1. Another drawback of the study is that it included women taking a range of daily doses of folic acid; in a random sample of the study, doses ranged from 100µg to 1000µg.

Milunsky *et al.* (21) reported the baseline prevalence of NTDs in the study population and the prevalence of NTDs in those who did not take folic acid, those who took folic acid in the first trimester only and those who took folic acid before conception and in the first trimester. Due to the baseline prevalence of NTDs in the UK currently being lower than the prevalence when this study was carried out (the study was also carried out in America), the prevalence for pregnancies affected by a NTD in England and Wales was used (prevalence of pregnancies affected by a NTD: 0.15% (22)) and the probability applied to the current population. These calculations resulted in the figures shown in Table 4.4. A number of

steps had to be taken to calculate the probability of pregnancy affected by a NTD occurring in the UK which are outlined below.

$$Risk_{Population} = \left(Proportion_{Never\ taking\ vit} \times Risk_{Never\ taking\ vit}\right) + \left(Proportion_{First\ trimester\ only} \times Risk_{First\ trimester\ only}\right) + \left(Proportion_{Before\ preg\ and\ in\ first\ trim} \times Risk_{Before\ preg\ and\ in\ first\ trim}\right)$$

Since we know the risk for the overall population, and also know the relative risks for each subgroup compared to each other (denoting the risk for those never taking vitamins as 'α'), we can show the equation as:

$$0.15\% = (0.21 \times \alpha) + (0.42 \times 0.69\alpha) + (0.37 \times 0.34\alpha)$$

Rearranging, this allows us to estimate the value of α (i.e. the risk for those never taking supplements) to be 0.24%. By application of the relative risk ratios, the risk for those taking supplements in the first trimester only (0.16%) and those taking supplements before pregnancy *and* during the first trimester (0.08%) can also be inferred.

The probability of pregnancies affected by a NTD in women taking folic acid in the first trimester of pregnancy (reported in (21)) was applied to the model subgroup of those taking folic acid before 10 weeks. For the model subgroup of those taking folic acid after 10 weeks of pregnancy (the current Healthy Start offering) the same benefit as not taking folic acid was applied. This assumption has been based on the World Health Organisation (WHO) guideline 2012 which indicated that there was no preventative effect of supplementing with folic acid on pregnancies affected by a NTD after 10 weeks:

> "Folic acid requirements are increased in pregnancy because of the rapidly dividing cells in the fetus and elevated urinary losses. **As the neural tube closes by day 28 of pregnancy, when pregnancy may not have been detected, folic acid supplementation after the first month of pregnancy will not prevent neural tube defects.**" *(WHO guideline, 2012 (23)).*

However, it should be noted that in the UK it is recommended that folic acid supplements should be taken from when a women begins to plan a pregnancy until the end of the 12th week of pregnancy, although it is common within the literature for there to be disparities in the definition of a trimester.

It was not possible to identify the probability associated with taking folic acid when planning a pregnancy, but not taking folic acid during pregnancy. This is because the majority of women would not supplement when planning a pregnancy and then stop when pregnant (except perhaps in cases where women experience sickness, precluding their ability to take tablets). Therefore, unsurprisingly, there were no studies identified that investigated this. Instead the model includes women taking folic acid supplements when planning a pregnancy *and* when pregnant up to 10 weeks and it also includes the subgroup women taking folic acid supplements when pregnant before 10 weeks (and not when planning). Although it was not possible to model the effects of women taking supplementation when planning a pregnancy only, it is also unlikely that the Healthy Start scheme would be supplied in this

way. As if it was, women would receive the Healthy Start vitamin supplements when they were planning a pregnancy, then, once pregnant would not receive them for 10 weeks and then would start receiving the supplements again after 10 weeks (as in the current targeted offering).

**Table 4.4: Probability inputs and sources – Folic acid**

| Folic acid - probability of NTDs | Not taking supplements | Taking supplements | Source |
|---|---|---|---|
| Pregnant women after 10 weeks | 0.24% | 0.24% | • Milunsky (1989) (21); • Morris and Wald (2007) (22)[a] |
| Women who conceive another child *within 4-11 months* | 0.24% | 0.08% | |
| Women who conceive another child *after 12 months* | 0.24% | 0.16% | |
| Women planning a pregnancy *(and up to 10 weeks)* | 0.24% | 0.08% | |
| Pregnant women before 10 weeks | 0.24% | 0.16% | |

a Both sources were used to calculate all probability inputs. Milunsky (1989) provided the probability of having a pregnancy affected by a NTD which was adjusted for the UK prevalence rate reported by Morris and Wald (2007).

Table 4.4 shows the first year postpartum subgroup broken down into 4 to 11 months and 12 months. This is included so that the benefits of folic acid can be applied to those women who may have conceived a second child within one year. For those who conceive a child within 4 to 11 months, the probability of taking supplements before and during pregnancy is applied as they will have been taking the supplements already provided for the first year post-partum before pregnancy and will also have the supplement for the first 28 days of pregnancy (as they will still be supplied for their first year postpartum). For those who have another child after 12 months they have the probability of taking the supplement before pregnancy only applied as they will not get supplements for the first 28 days from their postpartum supply.

### 4.3.2 Vitamin A

**Table 4.5: Probability inputs and sources – Vitamin A**

| Vitamin A - probability of being below LRNI | Not taking supplements | Taking supplements | Source |
|---|---|---|---|
| Infants and children over 6 months and under 4 years | 5.14% | 0.00% | NDNS(8), DNSIYC (10) |
| Infants aged 0 to 6 months | 0.12% | 0.00% | DNSIYC (10) |
| Infants and children over 4 years and under 5 years | 5.24% | 0.00% | NDNS (8) |

Table 4.5 outlines the inputs and sources of the probability of being below the vitamin A LRNI for each subgroup. The probability of being below the LRNI for those taking supplements was assumed to be zero.

For infants and children over 6 months and under 4 years data from the DNSIYC (10) and NDNS (8) were used. The DNSIYC reported the mean and standard deviation (SD) of

average daily intake from food sources only for vitamin A (as retinol equivalents) for those aged 7 months to 18 months, which was used to impute the number of people below the LRNI when not taking supplements. The NDNS reported the proportion of participants with daily intakes lower than the LRNI from food sources only, for those aged 1.5 to 3 years. A weighted average was calculated.

For infants and children aged 0 to 6 months, data from the DNSIYC was used for those aged 4 to 6 months. The DNSIYC reported the mean and SD of average daily intake from food sources only for vitamin A for those aged 4 to 6 months only.

For children aged 4 to 5 years, the NDNS raw data set reported the proportion of participants with daily intakes lower than the LRNI from food sources only for those aged 4 to 5 years.

### 4.3.3 Vitamin C

Table 4.6 outlines the inputs and sources of the probability of being below the vitamin C LRNI for each subgroup. The probability of being below the LRNI for those taking supplements was assumed to be zero.

For the infants and children subgroups the same data were used as that described in Section 4.3.2 above, though specific to vitamin C.

For pregnant women, women up to 12 months postpartum and women planning a pregnancy, data were used from the NDNS which reported the proportion of non-pregnant women in the general population with daily intakes lower than the LRNI from food sources only. The survey reported this for women aged 19 to 64 years. However, analysis of the raw data provided this input for those aged 19 to 44 years. In the absence of any more appropriate data, the assumption was applied that the probability of being below the LRNI if not taking supplements was the same for pregnant women as for non-pregnant women.

**Table 4.6: Probability inputs and sources – Vitamin C**

| Vitamin C - probability of being below LRNI | Not taking supplements | Taking supplements | Source |
|---|---|---|---|
| Pregnant women after 10 weeks | 1.55% | 0.00% | NDNS raw data (8) |
| Women with a child up to 12 months | 1.55% | 0.00% | NDNS raw data (8) |
| Infants and children over 6 months and under 4 years | 0.71% | 0.00% | NDNS (8), DNSIYC (10) |
| Women planning a pregnancy *(and up to 10 weeks)* | 1.55% | 0.00% | NDNS raw data (8) |
| Pregnant women before 10 weeks | 1.55% | 0.00% | NDNS raw data (8) |
| Infants aged 0 to 6 months | 0.00% | 0.00% | DNSIYC (10) |
| Infants and children over 4 years and under 5 years | 0.00% | 0.00% | NDNS (8) |

### 4.3.4 Vitamin D

The approach taken for vitamin A and C could not be adopted for vitamin D as there was no defined LRNI.

In the absence of national survey data, data from Moy *et al.* (2012) (5) and McGee and Shaw (2013) (19) were used. Both studies describe the same intervention of universal supplementation rolled out in Birmingham. Moy *et al.* (2012) (5) reported a before-intervention uptake (3%) and McGee and Shaw (2013) (19) reported an after intervention uptake (20% for children under 5 and 23% for pregnant and breastfeeding women). The studies also reported the incidence of symptomatic vitamin D deficiency.

Modelling of the consequences of increased uptake in these two subgroups was based on the prevalence of presenting cases of symptomatic vitamin D deficiency, before and after the intervention, and was taken from Moy *et al.* (2012) (5). The annual incidence of symptomatic vitamin D deficiency was 0.12% before the intervention and 0.049% after the intervention. These data were only available for children, so in the absence of any other data, the assumption was made that the same effects applied to women. Based on these two data points, both an exponential function and a linear function were applied (to allow the model user to select which function to use) to the percentage of patients with symptomatic vitamin D deficiency based on the percentage uptake of vitamin D selected earlier in the model. Table 4.7 shows the probability of having symptomatic vitamin D deficiency using the exponential function and the national survey data in the uptake inputs.

Vitamin D deficiency can be a cause of hypocalcaemic seizures or fits, particularly in new-borns. Although these are one aspect of symptomatic vitamin D deficiency which is the outcome measure included in the model, the ERG debated whether hypocalcaemic seizures due to vitamin D deficiency should be separately modelled and requested information on the incidence of this condition. A paper was identified which reported the incidence to be 3.49 per million children in UK and Ireland (Basatemur and Sutcliffe 2014). Of these, 95% occurred in children aged from 0-2 years with a significantly higher incidence in males and in children from South Asian or Black communities compared to white children.

ERG members were aware that if left untreated, hypocalcaemic fits can in extreme cases, lead to permanent neurological damage with symptoms that could be considered similar to those of cerebral palsy. They recognised the considerable lifetime implications for the children and their families and noted the very large costs this would incur to public sector for each case. However it was not possible to identify data on the proportion of children suffering a hypocalcaemic fit due to vitamin D deficiency, that go on to develop permanent neurological damage, or the costs associated with treating and caring for children who do so. On the advice of the ERG, one of the authors of the above paper was contacted. He advised that the number of cases of hypocalcaemic fits which result in severe neurological damage is very small in comparison to the incidence of other conditions caused by a low vitamin D status that affect bone health in later childhood and adulthood (Personal communication – Professor Sutcliffe). As these conditions are already included in the model, specific data on hypocalcaemic seizures have not been added to the analysis.

**Table 4.7: Probability inputs and sources – Vitamin D**

| | Targeted | Universal | No provision under Healthy Start | Source |
|---|---|---|---|---|
| Pregnant women after 10 weeks | 0.021% | 0.008% | N/A | • Moy *et al.* (2012) (5), • McGee and Shaw (2013) (19) |
| Women with a child up to 12 months | 0.026% | 0.011% | N/A | |
| Infants and children over 6 months and under 4 years | 0.097% | 0.045% | N/A | |
| Women planning a pregnancy *(and up to 10 weeks)* | N/A | 0.020% | 0.048% | |
| Pregnant women before 10 weeks | N/A | 0.008% | 0.021% | |
| Infants aged 0 to 6 months | N/A | 0.044% | 0.095% | |
| Infants and children over 4 years and under 5 years | N/A | 0.039% | 0.084% | |

## 4.4 COST INPUTS

As outlined in Section 2.1, the model allows various cost perspectives to be taken.

As previously mentioned, two scenarios of universal supplementation were considered. For the sake of clarity, this is re-capped below.

Scenario 1 – The current scheme is moved to a universal offering within the current parameters of the scheme (all pregnant women from 10 weeks; women with a child under 12 months; and children over 6 months and under 4 years);

Scenario 2 - The current scheme is moved to a universal offering for all current and extended subgroups (All women planning a pregnancy; pregnant women; women with a child aged under 12 months; infants aged from 0 to 6 months and children aged from 6 months to 5 years).

Table 4.8 below summarises the cost inputs and the sources of these inputs.

**Table 4.8: Cost inputs and sources**

| Input | Source |
|---|---|
| **Intervention cost** | |
| Cost of Healthy Start vitamin supplements | Department of Health |
| One off set-up costs | YHEC costing template interviews, DH data |
| Annual cost of distribution and running scheme locally | YHEC costing template interviews |
| Annual cost of distribution and running scheme centrally | DH data |
| **Treatment cost inputs*** | |
| Cost of treating symptomatic vitamin D deficiency | Zipitis *et al*. (2006) |
| Cost of pregnancy affected by a NTD | Morris and Wald (2007) (22), Bowles *et al.* (2014) (24), Jentink *et al.* (2008) (25), Tilford *et al.* (2005) (26), NHS Reference Costs |
| Cost of a day of lost productivity | ONS (2014) (27) |

* All costs more than one year old have been converted to 2014 prices.

### 4.4.1 Intervention Cost Inputs

The intervention cost inputs included the price of purchasing the Healthy Start vitamin supplements and the costs associated with distributing the vitamins and running the Healthy Start vitamin supplements scheme.

#### 4.4.1.1 Cost of Healthy Start vitamin supplements

The model includes an option to input the increase in the uptake of Healthy Start vitamin supplements. The cost of Healthy Start vitamin supplements were assumed to be £0.74 per pack of women's tablets and £1.38 per pack of children's drops' based on communication with DH. The cost of Healthy Start vitamin supplements was applied for one year's supply.

#### 4.4.1.2 One-off set-up costs

The set-up cost for the targeted scenario (as the scheme currently stands) was assumed to be zero both nationally and locally as this scheme was already running. The DH reported that there were unlikely to be any up-front set-up costs of moving to the universal scheme (scenario 1 and 2). The model includes the incremental cost of setting up the universal scheme (scenario 1 and 2). This was varied within sensitivity analysis. Therefore, scenarios were considered whereby the cost of set-up of the targeted scheme (as the scheme currently stands) was implied not to be equal to zero.

#### 4.4.1.3 Annual cost of distribution and running scheme

##### 4.4.1.3.1 Targeted scenario (as the scheme currently stands)

Since we are looking at the additional cost of running the HSV scheme, we can disregard the annual cost of the targeted scheme and consider only the incremental cost of the relevant universal scheme each year. The DH reported that the cost of the vitamin supplement part of the whole Healthy Start scheme is negligible. Although the cost to local government was said to be zero as the vitamins are reimbursed, there will be some costs from staff time spent running the scheme and through vitamin wastage and not claiming back the costs of the scheme. Unfortunately, the costing templates that were returned were only partially completed and this information was not provided.

##### 4.4.1.3.2 Universal scenario (scenario 1 and 2)

The annual cost of running the scheme if a universal scenario was applied has been provided by the DH. The DH gave a cost per extra application and a cost per extra vitamin coupon re-issue. The ERG discussed that it is not yet clear how a universal scheme would be run and how the vitamins would be distributed. It is possible that coupons would no longer be issued by the DH. Graph 5.10 of the sensitivity analysis shows how the ICER would be affected if the cost was £0 (i.e. if it was not necessary for the DH to issue coupons).

As the costing templates were partially completed, YHEC have carried out detailed interviews with staff in Public Health Lewisham and Birmingham Community Healthcare NHS Trust to determine the costs of running a universal scheme. The costs from Public Health Lewisham were used in the base case analysis because the data is more robust as it is based on electronic issuing data. In Lewisham, a card scheme is in operation, whereby all participants carry a chipped card which brings up their record at any participating outlet distributing vitamin supplements. However, not all areas offering Healthy Start supplements universally would use this approach and will have different cost structures.

The costs provided by Lewisham included pharmacy costs, ordering and distribution, card readers and electronic cards including licence fee, training and promotion. The costs were categorised into fixed and variable costs (fixed costs in this context are defined as the ones that do not change depending on the number of people in the scheme, such as, annual licensing fees). This gave a set-up cost for the first year when scaled up for England of over £[redacted] and a variable cost to local government of £[redacted] per person (this does not include the cost of vitamins as these will be reimbursed). Costs in subsequent years were £[redacted] (fixed) and £[redacted] per person (variable). The effect of costs in subsequent years on the ICER has been examined in sensitivity analyses graphs 5.7 and 5.8. The costs provided from Birmingham included set-up costs, publicity, contract with a distribution centre, staff time, vitamin wastage, licensing fees and consumables. The costs provided were a best estimate based on the data that were available. The fixed costs for Birmingham were £113 per year in the first year and subsequent years (giving a cost across all CCGs of £23,843). The variable costs (based on an estimate of the number of people that vitamin supplements were provided to) were £12.72 per person in the first year and £10.08 in subsequent years.

It is important to note that these costs are an estimate and they may vary by area. The two schemes differ considerably, because Lewisham has instituted a smart-card scheme that appears to have increased its fixed costs substantially but decreased its per-person.

Further, because cost inputs for 'per person' costs of running the *current* scheme were not available, the incremental cost per person is likely to be an overestimate. This was a conservative approach, because the differential cost was likely to be lower which would make the universal scheme more cost-effective. Another unknown was how the vitamins would be distributed to both women planning a pregnancy and those less than 10 weeks pregnant, as this would require a new route to target women this early on. It is likely that distribution costs might be different for women planning a pregnancy, but it is not known by how much. Therefore, sensitivity analysis examines how varying this cost impacts upon on the model result. In the model an assumption is applied that the costs of incorporating new groups would be the same as for those in the existing scheme.

### 4.4.2 Treatment Cost Inputs

Treatment costs only apply to vitamin D and folic acid, since no functional outcomes have been identified for vitamins A and C.

#### 4.4.2.1 Cost of treating symptomatic vitamin D deficiency

The cost of treating a single case of symptomatic vitamin D deficiency was taken from Zipitis *et al.* (2006) (6) and was converted to 2012/2013 costs using the Hospital and Community Health Services Index from PSSRU's Unit Costs of Health and Social Care 2014. This was estimated to be £3,021.

#### 4.4.2.2 Cost of a pregnancy affected by a NTD

The cost of a pregnancy affected by a NTD is shown in Table 4.9. The proportion of pregnancies affected by a NTD that result in termination, anencephaly or spina bifida were taken from Morris and Wald (2007) (22). The authors report the prevalence of pregnancies affected by a NTD and the outcome of the pregnancy in England and Wales from 1964 to 2004 based on ONS data. More recent figures reporting the proportion of pregnancies affected by a NTD that resulted in termination from the British Isles Network of Congenital Anomaly Registers (BINOCAR) (28) were identified. These figures are similar to those in Table 4.9. 77.98% of pregnancies affected by a NTD resulted in termination, 3.06% resulted in still birth, 17.13% resulted in a live birth and 1.83% were classed as miscellaneous. These data were only available for 36% of the population. Due to the similarity with Morris and Wald (2007) and the potential problems with the data, these figures were not used in the base case; however, sensitivity analysis explores the effect of varying the number of pregnancies resulting in termination (Section 5.5).

**Table 4.9: Pregnancy affected by a NTD lifetime costs – healthcare system**

| | Proportion | Cost per case |
|---|---|---|
| Terminations | 80.00% | £890 |
| Birth - anencephaly | 6.67% | £0 |
| Spina bifida | 13.33% | £94,458 |
| **Total cost per case of pregnancy affected by a NTD** | **100.00%** | **£13,306** |

The cost of a termination was taken from NHS Reference Costs 2012/13 as the cost of a medical termination of a pregnancy at 14 to 20 weeks. No costs were applied to a birth of a baby with anencephaly as many result in stillbirths and babies from live births are not given any treatment, only comfort measures, with most dying within 24 hours.

The lifetime cost of spina bifida was calculated from Bowles (2014) (24) who reported the direct healthcare costs per year for a person with spina bifida to be 4,532 Euros. Jentink *et al.* (2008) (25) reported the average life expectancy for a person with spina bifida to be 63.74 years. This cost was converted into pounds using the exchange rate on 31 October 2014 resulting in a cost of £3,580 per year and was discounted at a rate of 3.5% over the lifetime, resulting in a lifetime cost to the healthcare system of £94,458 (Table 4.9).

The extra societal cost of a pregnancy affected by a NTD has also been estimated (Table 4.10). This cost consists of the societal costs associated with sick days and caregiver time. Tilford (2009) (26) (from Yi *et al.,* 2011 (29)) reported that the caregiver of a child with spina bifida works between 7.5 and 11.3 hours less per week in the paid workforce (US study). Therefore, one day per week (52 days a year) has been assumed lost for children and young adults aged 0-18 years.

Bowles (2014) (24) reported that 10.84 sick days are taken per year by a person with spina bifida, assumed from age 18 until 60. Each lost day of work was assigned the cost of median gross weekly earnings (ONS, 2014 (27)) at £103.40 per day. The costs included in the societal perspective were discounted at a rate of 3.5% over the lifetime.

**Table 4.10: Pregnancy affected by a NTD lifetime costs – Societal (additional to healthcare system costs)**

| | Proportion | Cost |
|---|---|---|
| Terminations | 80.00% | £890 |
| Birth - anencephaly | 6.67% | £0 |
| Spina bifida | 13.33% | £87,180 |
| **Total cost per case of pregnancy affected by a NTD** | **100.00%** | **£11,624** |

## 4.5 UTILITY INPUTS

### 4.5.1 Spina Bifida

There were two sources for the QALYs lost per case of spina bifida, and the model user can select the preferred source.

The first source of QALYs gained over a lifetime for a person with spina bifida was Jentink *et al.* (2008) (25). Jentink reported the proportion of people with three types of spina bifida; thoracic lesion, lumbar lesion or sacral lesion. For each of these the life expectancy and utility values at ages 0-10, 11-21 and >21 years was reported. The QALYs for each type of spina bifida were calculated, these were then discounted at a rate of 3.5% over the lifetime and a weighted average of these was taken. These data are presented in Table 4.11.

**Table 4.11: QALYs for people with spina bifida – Jentink *et al.* (2008)**

| | | | Utility | | | Total discounted QALYs |
|---|---|---|---|---|---|---|
| **Spina bifida type** | **Proportion** | **Life expectancy** | **0-10 yrs** | **11-21 yrs** | **>21 yrs** | |
| Thoracic lesion | 28.00% | 40 | 0.30 | 0.18 | 0.30 | 5.94 |
| Lumbar lesion | 62.00% | 72 | 0.45 | 0.42 | 0.42 | 11.69 |
| Sacral lesion | 10.00% | 79 | 0.83 | 0.73 | 0.79 | 21.86 |
| | | | | **Weighted average** | | **11.10** |

The second source of QALYs for a person with spina bifida was reported by Grosse *et al.* (2008) (30). Grosse carried out an economic evaluation and reported that the utility for children and adolescents with spina bifida was 0.55; the paper reported that in combination with life expectancy this gives an average QALY value of 13.7.

These two sources providing lifetime QALY estimates for people with spina bifida were compared with the discounted lifetime QALYs of a person without spina bifida to determine the difference (i.e. total QALYs lost).

The lifetime QALYs of a person without spina bifida were calculated using population norms by age bracket (EuroQol UK Population norms (31)) adjusted by mortality rate (ONS National life tables 2011-13 (32)) and discounted at a rate of 3.5% over the lifetime, giving lifetime QALYs of 25.00.

Using the data from Jentink *et al.* (2008) (25) resulted in 13.91 lost QALYs per case of spina bifida, using Grosse *et al.* (2008) resulted in lost QALYs per case of 11.25. The model was run with utility values from Jentink *et al.* (2008) as this source provided more detail and this was also the source used for average life expectancy in the model.

The model also included the societal value of lost QALYs from caregivers' time for the societal perspective. Tilford *et al.* (2005) (26) reported the utility for a caregiver of a child with spina bifida as 0.760. This was assumed to apply for 18 years and results in 1.87 additional lost QALYs.

### 4.5.2 Terminations

The utility loss, or reduction in quality of life, for the mother associated with termination was also included in the model. As shown in Table 4.10, a paper by Jentink *et al.* (2008) reported that 80% of pregnancies affected by a NTD result in a termination. The utility value associated with elective termination was reported in Harris (2004) (33). Harris reported the utility associated with testing a foetus during pregnancy with normal results and an unaffected birth (0.923) and the utility associated with testing the foetus, elective abortion and future births are unaffected (0.836). The disutility was calculated (0.087). The assumption was made that the disutility applied for 6 months, gradually increasing to the utility associated with normal results after testing a foetus. The assumption that the disutility applies for 6 months was an arbitrary assumption made due to a lack of data. The amount of time that QOL loss occurs due to a termination would vary person to person. This assumption resulted in a QALY loss associated with elective termination of 0.022 which was applied to each termination in the model.

There were no data identified that gave a disutility associated with having a baby with anencephaly, therefore, the same disutility as that associated with a termination was applied with the assumption that having a baby with anencephaly has at least the same utility loss as having a termination over the same duration.

# Section 5: Results

## 5.1 BASECASE RESULTS

In order to make this section clearer, the definitions of current subgroups and extended subgroups are reiterated below (these are also outlined in Section 2.1):

- Population subgroups included in the current Healthy Start offering:
  - Pregnant women after 10 weeks;
  - Women with a child up to 12 months;
  - Infant and children over 6 months and under 4 years.
- Extended subgroups:
  - Women planning a pregnancy (and before 10 weeks);
  - Pregnant women before 10 weeks;
  - Infants aged 0 to 6 months;
  - Infants and children over 4 years and under 5 years.

As previously mentioned, two scenarios of universal supplementation were considered and are reported in the results section.

Scenario 1 – The current scheme is moved to a universal offering within the current parameters of the scheme (all pregnant women from 10 weeks; women with a child under 12 months; and children over 6 months and under 4 years;

Scenario 2 - The current scheme is moved to a universal offering for all current and extended subgroups (All women planning a pregnancy; pregnant women; women with a child aged under 12 months; infants aged from 0 to 6 months and children aged from 6 months to 5 years.

### 5.1.1 Offering Healthy Start Supplements Universally to All of the Current Subgroups (Scenario 1)

**Key messages from Offering Healthy Start Supplements Universally to All of the Current Subgroups (Scenario 1):**

- The model shows that offering Healthy Start supplements universally to all of the current subgroups is not cost-effective using the accepted £20,000 threshold for the ICER;
- The ICER for this extension is £620,898 per QALY.

Table 5.1 shows the results if the offering were to be extended universally to the current subgroups but to none of the extended subgroups.

**Table 5.1: Results for all current subgroups (Scenario 1)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £4,975,405 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £4,631,582 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £30,758,128 | £26,372,547 | -£4,406,434 |
| **Total incremental cost** | | | **£7,874,978** |
| QALYs lost (pregnancy affected by a NTD) | 3,635 | 3,623 | -13 |
| **Total QALYs gained** | | | **13** |
| **ICER** | | | **£620,898** |
| Number of people below vitamin A LRNI | 113,316 | 92,430 | -20,886 |
| Number of people below vitamin C LRNI | 29,123 | 21,860 | -7,263 |

* The incremental cost only was calculated.

The results show that, with the current model inputs, moving to a universal scheme within the current subgroups (pregnant women after 10 weeks, women with a child up to 12 months and infants and children over 6 months and under 4 years) would not be cost-effective, using the accepted £20,000 threshold for the incremental cost-effectiveness ratio (ICER).

The ICER is very high at £620,898 per QALY. The results table shows that the incremental cost of implementing the scheme is over £7 million. The number of QALYs gained is low. There are two main reasons as to why the ICER is so high. The first is that it has not been possible using conventional means to ascribe a QALY gain for vitamins A, C and D with any degree of accuracy. These benefits are difficult to quantify as well as being small and diffused among a large number of women and children (the effect of adding a QALY benefit for vitamins A, C and D has been explored in a sensitivity analysis as a hypothetical exercise in Section 5.3.4). The second is that the gain of 13 QALYs does not arise from the reduction of NTDs in the present pregnancy, as the folic acid supplement occurs too late to be of benefit. It occurs because of a reduction in pregnancies affected by a NTD for subsequent pregnancies that occur within one year of the birth of the child for which the supplement has been provided to the mother.

### 5.1.2 Results for Extended Subgroups Only (Additional Analysis)

These results are for information only and do not answer the research questions directly but are included to aid with understanding of the results

**Key messages from the Results for Extended Subgroups Only:**

- The model shows that universal provision to only the extended subgroups is cost-effective overall;
- The model shows that two subgroups are cost-effective when assessed on their own – Women planning a pregnancy (and before 10 weeks pregnant) and pregnant women before 10 weeks;
- Two subgroups are not cost-effective when assessed on their own – Infants aged 0 to 6 months and Children aged 4 to 5 years. These two subgroups are at extra cost for no extra benefit under the assumption that the benefit of vitamin D cannot be quantified.

**Table 5.2: ICER for extended subgroups only**

| Subgroup combination. Universal offering is extended to*: | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Women planning (and before 10 weeks pregnant) | -£989,352 | 737 | **Dominant** |
| Pregnant women before 10 weeks | £1,683,725 | 230 | **£7,126** |
| Infants aged 0 to 6 months | £2,668,015 | 0 | Infinite** |
| Children aged 4 to 5 years | £3,363,541 | 0 | Infinite** |
| All extended subgroups | -£306,646*** | 737 | **Dominant** |

* Green (and bold) text indicates that the ICER is below £20,000. Red text indicates that the ICER is over £20,000;

****** Extra cost for no extra benefit.

*** The incremental costs of all extended subgroups is not the sum of the incremental cost for each subgroup. This is because when the offering is extended to all subgroups, the set-up (or fixed) cost of the intervention is only included once. Further, women planning (and before 10 weeks pregnant) is inclusive of pregnant women before 10 weeks.

Table 5.2 shows the ICER when the universal offering is provided to the extended subgroups only (without combining with the current subgroups). Similarly to the results reported for the combined subgroups (Scenario 2), offered universally to the extended subgroups without also being offered universally to the currently targeted groups is most cost-effective when the subgroup 'women planning a pregnancy and before 10 weeks pregnancy' is included. The table shows that the ICER is lower when this subgroup is included due to the large number of QALYs gained from the prevention of pregnancies affected by a NTD and due to the cost savings made from preventing pregnancies affected by a NTD and symptomatic vitamin D deficiency. Although the model results do not report QOL benefits for the other vitamins (vitamins A, C and D) there may still be some QALY gains. However, suitable quantitative information was not available to include this in the model. This is explored in more detail in Section 5.3.4. Further, in the absence of any practical experience of such a scheme, it was assumed that the cost of distributing to the extended groups was the same as for the current subgroups. This is explored in sensitivity analyses Graphs 5.7 and 5.8. The detailed breakdown of each combination is shown in Appendix C.

### 5.1.3 Results for Offering Healthy Start Supplements to the Extended Subgroups and to the Currently Targeted Subgroups, on a Universal Basis (Scenario 2)

**Key messages from the Results for Offering Healthy Start Supplements to The Extended Subgroups and to the Currently Targeted Subgroups, on a Universal Basis (Scenario 2):**

- The model shows that offering Healthy Start supplements to the extended subgroups and to the currently targeted subgroups, on a universal basis is cost-effective;
- These results are driven by the inclusion of women planning a pregnancy and less than 10 weeks pregnant;
- When offering Healthy Start supplements on a universal basis, one extended subgroup when combined with current subgroups (scenario 1) is cost-effective when assessed on its own – Women planning (and before 10 weeks pregnant);
- When offering Healthy start supplements on a universal basis, three extended subgroups are not cost-effective when assessed with current subgroups (scenario 1) – Pregnant women before 10 weeks, Infants aged 0 to 6 months and Children aged 4 to 5 years.

Table 5.3 shows the ICER when the offering is extended universally to various combinations of the extended subgroup. The detailed breakdown of each combination is shown in Appendix C.

**Table 5.3: ICER for extended subgroups combined with current subgroups when the Healthy Start scheme is offered on a universal basis (Scenario 2)**

| Subgroup combination. Universal offering is extended to: | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Current subgroups | £7,874,978 | 13 | £620,898 |
| Current subgroups + women planning (and before 10 weeks pregnant) | £4,211,201 | 750 | **£5,618** |
| Current subgroups + pregnant women before 10 weeks | £6,839,279 | 243 | £28,185 |
| Current subgroups + infants aged 0 to 6 months | £7,868,568 | 13 | £620,392 |
| Current subgroups + children aged 4 to 5 years | £8,564,095 | 13 | £675,230 |
| Current subgroups + all extended subgroups | £4,893,907 | 750 | **£6,528** |

* Green (and bold) text and background indicates that the ICER is below £20,000. Red text (not bold) and background indicates that the ICER is over £20,000. Amber text and background indicates that the ICER is between £20,000 and £30,000.

The table shows that as long as women planning a pregnancy and before 10 weeks pregnant are included it is cost-effective to move to a universal offering. The model shows that moving to a universal offering is not cost-effective if supplementation is offered to the current subgroups plus pregnant women before 10 weeks (without also including women

planning a pregnancy) or the current subgroups plus infants aged 0 to 6 months or the current subgroups plus children aged 4 to 5 years.

The infants and children subgroups do not gain QALYs through the prevention of NTD as this outcome is not relevant to this group. In addition it was not possible to assign QALYs associated with being below the LRNI (for vitamins A and C) and with having symptomatic vitamin D deficiency. The ICER is lower for current subgroups plus pregnant women before 10 weeks as when this group take folic acid vitamin supplements this does prevent some cases of pregnancies affected by a NTD (but not as many as when also taking it when planning a pregnancy) in the economic model. However, combining this with the currently targeted subgroups (but not the extended subgroups) is not enough to bring the ICER below £20,000.

The model shows that it is cost-effective to offer supplementation universally to the currently targeted groups plus all of the extended subgroups in combination. This is driven by the inclusion of women planning a pregnancy (and before 10 weeks pregnant). Although it is not cost-effective to extend the universal offering to the current subgroups alone or the current subgroups combined with the extended groups of infants and children only or pregnant women before 10 weeks only. As long as the subgroup 'women planning a pregnancy (and before 10 weeks pregnant)' is included, offering supplementation to the other subgroups in addition increases the ICER only slightly.

When the subgroup 'women planning a pregnancy (and before 10 weeks pregnant)' is included, all the benefits of preventing NTDs are included, and these benefits outweigh the incremental costs incurred in the other groups. (The precautionary principle applies here which argues that the cost of supplying the additional tablets is small but may reduce some significant harm and is unlikely to cause any harm). The incremental costs of including vitamins C and D in the women's supplement within the model is likely to be negligible and the incremental cost of supplying children's vitamins is low enough for the whole scheme to remain cost-effective when the 'women planning a pregnancy (and before 10 weeks pregnant)' subgroup is included. Further, the cost savings associated with preventing cases of symptomatic vitamin D deficiency also contributes to making the intervention cost-effective.

When all of the subgroups and extended subgroups are included, vitamin D supplementation contributes around half of the total cost savings. Although adding the extended infants and children subgroups does not give any QALY gain in the model, it does contribute added savings from preventing cases of vitamin D deficiency. The cost-effectiveness is driven by a combination of:

- QALY gains from preventing pregnancies affected by a NTD;
- The cost-savings associated with preventing pregnancies affected by a NTD;
- Preventing cases of symptomatic vitamin D deficiency.

It is important to emphasise that supplementation with vitamins A, C and D may result in some QOL benefits but as these could not be quantified, the model only includes QOL measures for pregnancies affected by a NTD. Although adding the other subgroups

increases the ICER, there is an added benefit of bringing many more people above the vitamin A and C LRNI.

It was not possible to model a 'spill-over' effect in which supplementation use increases in those in the currently targeted groups, perhaps as a result of increased awareness of the Healthy Start vitamin supplements. Using the current model structure, it was not possible to disentangle from which group (currently targeted or not) the new level of uptake was from.

## 5.2 SENSITIVITY ANALYSIS (SCENARIO 2)

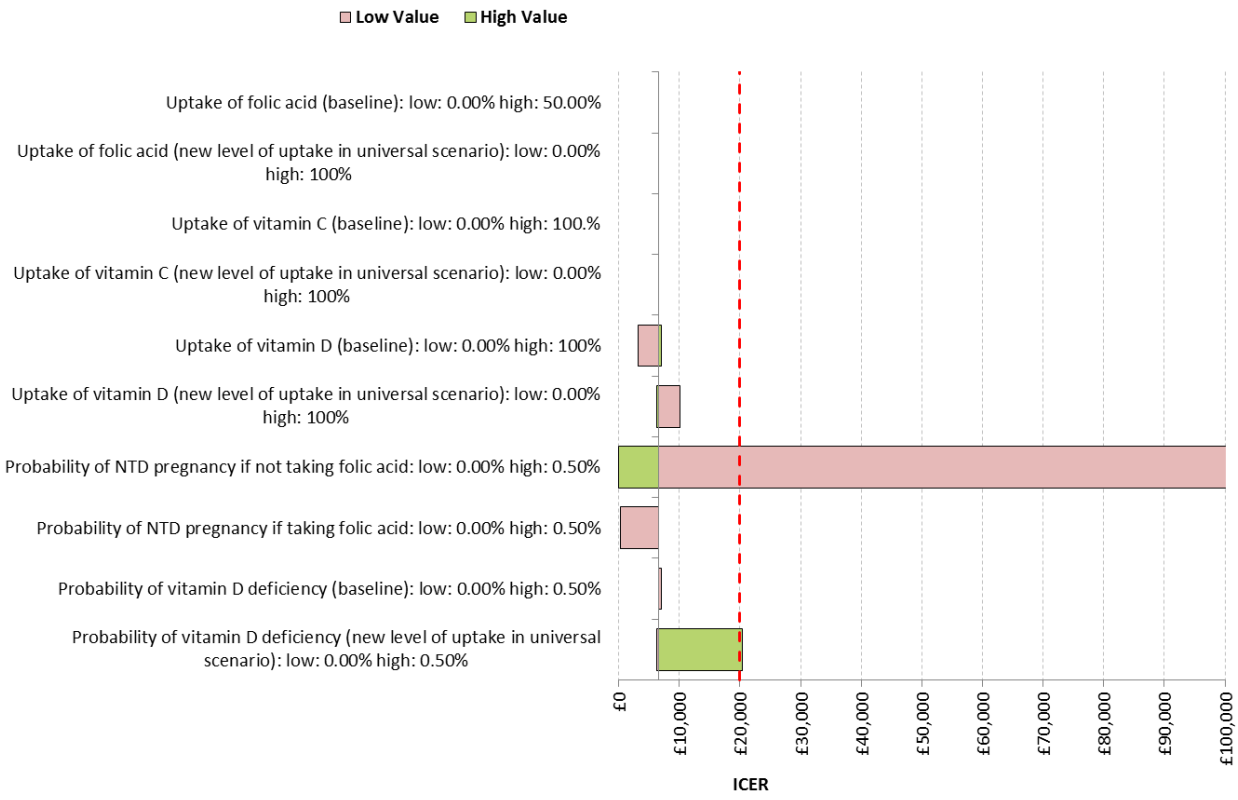
Extensive univariate sensitivity analyses have been carried out, whereby one parameter within the model is varied in isolation to assess its impact on the model's results. Tornado diagrams allow many univariate sensitivity analyses to be reported in one diagram. Presenting the univariate sensitivity analyses in a tornado diagram allows the key drivers of the model to be identified as many univariate sensitivity analyses are viewed alongside each other. An explanation of how to read and interpret the tornado diagrams is given in Appendix D which should be read first if the reader is not conversant with this notion.

**Key messages from the Univariate Sensitivity Analysis of Uptake and Effectiveness Inputs on the Results for Universally offering HS supplements to the currently targeted groups plus the extended subgroups (Scenario 2; Base Case ICER = £6,528):**

- Where the probability of pregnant women after 10 weeks having a pregnancy affected by a NTD if not taking folic acid is below 0.15% (i.e. less than 1.5 in 1,000 pregnancies) the model shows that the intervention is no longer cost-effective;
- Where the probability of vitamin D deficiency in the new (universal) level of uptake for infants and children over 6 months and under 4 years is above 0.2% the intervention is no longer cost-effective;
- Where the uptake of folic acid in the new (universal) level of uptake for women planning a pregnancy and up to 10 weeks pregnant is below 30%, the intervention is no longer cost-effective;
- In all other univariate sensitivity analyses conducted around uptake and effectiveness inputs, the universal offering remains cost-effective for the ranges considered.

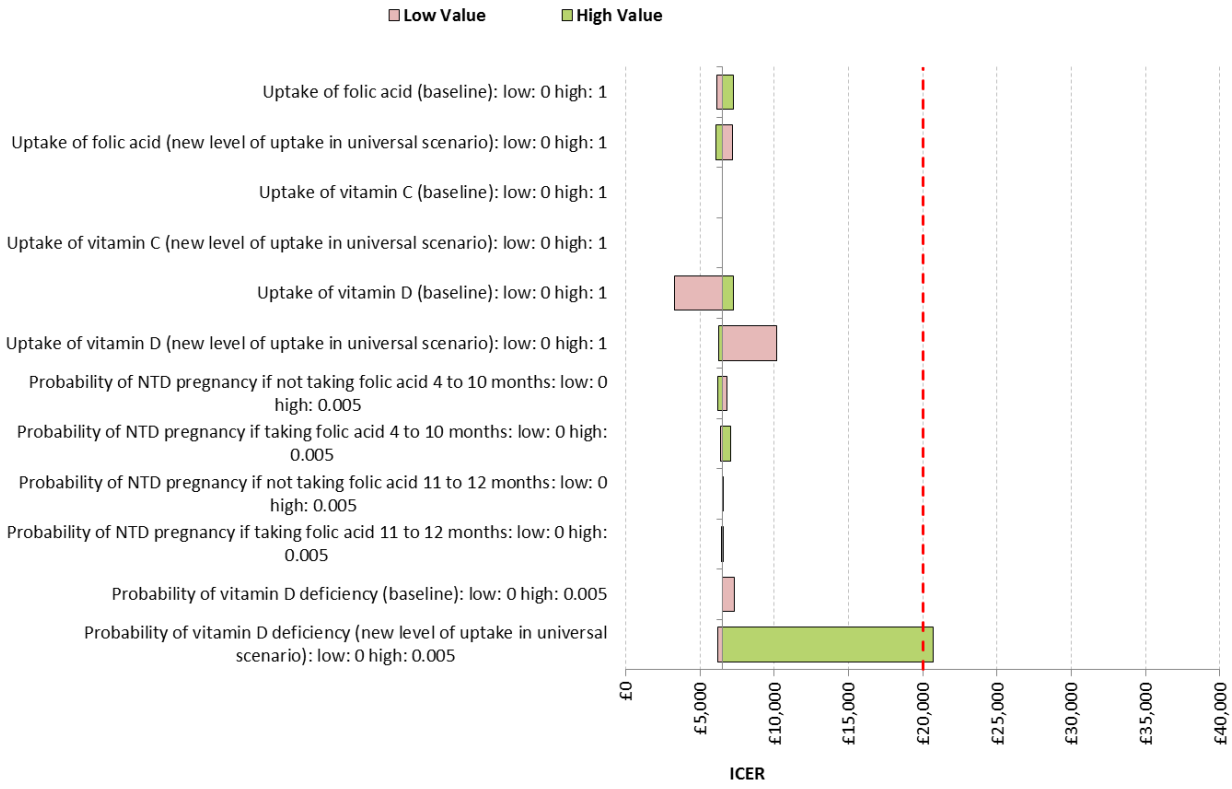
Graphs 5.1 to 5.6 illustrate the univariate sensitivity analyses for uptake and effectiveness in tornado diagrams. In each graph the parameters for one of the sub groups is varied and the results shown are the impact on cost effectiveness for Scenario 2 overall. In each of these graphs, the results displayed are for scenario 2 overall (all of the potential subgroups to extend the universal offering to have been included). Each graph displays a dotted line which shows a cost-effectiveness threshold of £20,000.

**Graph 5.1: Pregnant women after 10 weeks**




The tornado diagram shows that, as mentioned in the overall results section, the probability of pregnancies affected by a NTD is a key driver of the model results. Varying the probability of pregnancy affected by a NTD accounts for any changes in prevalence compared with the source used in the model. When the probability of a pregnancy affected by a NTD when not taking folic acid is low, the ICER for the overall scheme (scenario 2) increases past the cost-effectiveness threshold of £20,000. Threshold analyses show that the £20,000 threshold would be crossed when the probability of a pregnancy affected by a NTD if not taking folic acid is under approximately 0.15%. The bar showing the probability of pregnancy affected by a NTD if taking folic acid does not display a high value, because when the maximum value is used (0.5%), the ICER shows that the intervention is 'less effective'. This occurs as folic acid no longer effectively reduces the risk of NTD. The diagram also shows that there is no difference to the cost-effectiveness depending on uptake of folic acid in this group, because the baseline probability of pregnancies affected by a NTD is the same for those taking and not taking folic acid (because when the folic acid is taken, it is after 10 weeks pregnancy).

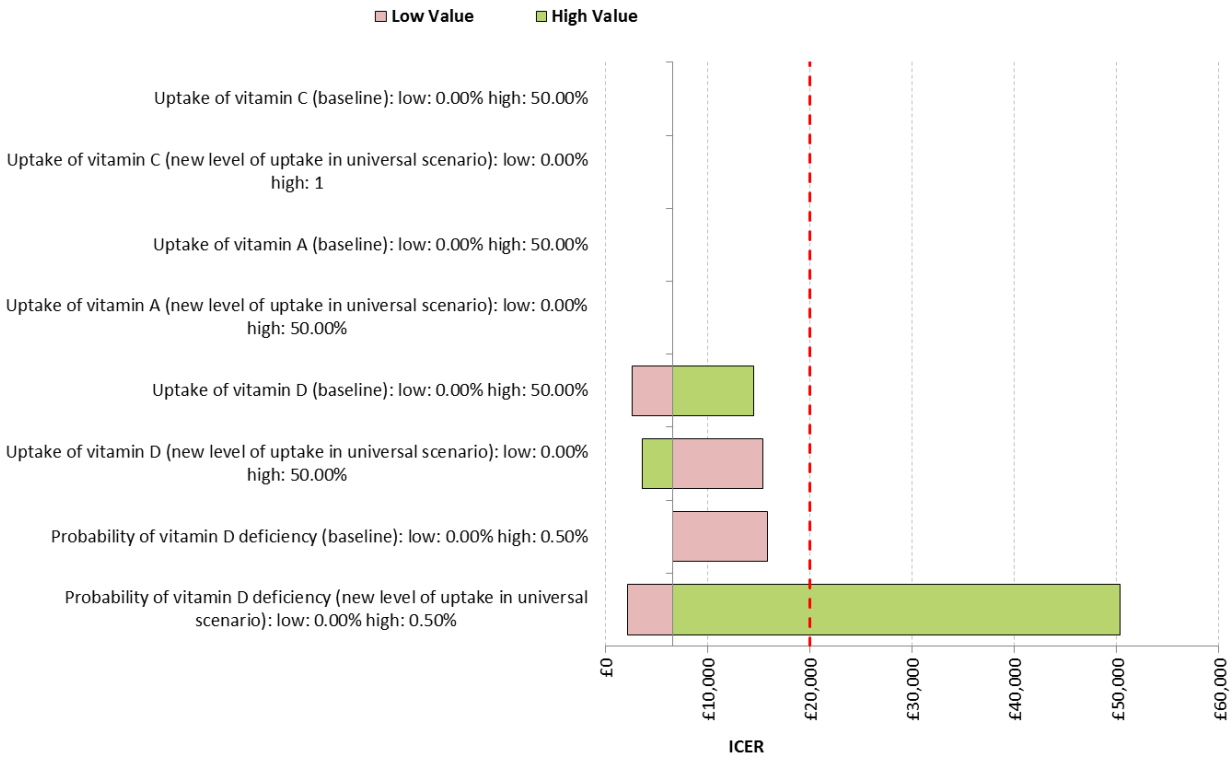
**Graph 5.2: Women with a child up to 12 months**




In this population subgroup, the folic acid effectiveness rate has a much smaller effect on the results for the overall scheme (scenario 2) because only a small proportion of this subgroup would benefit from folic acid supplementation (those who have a further pregnancy within one year of giving birth).

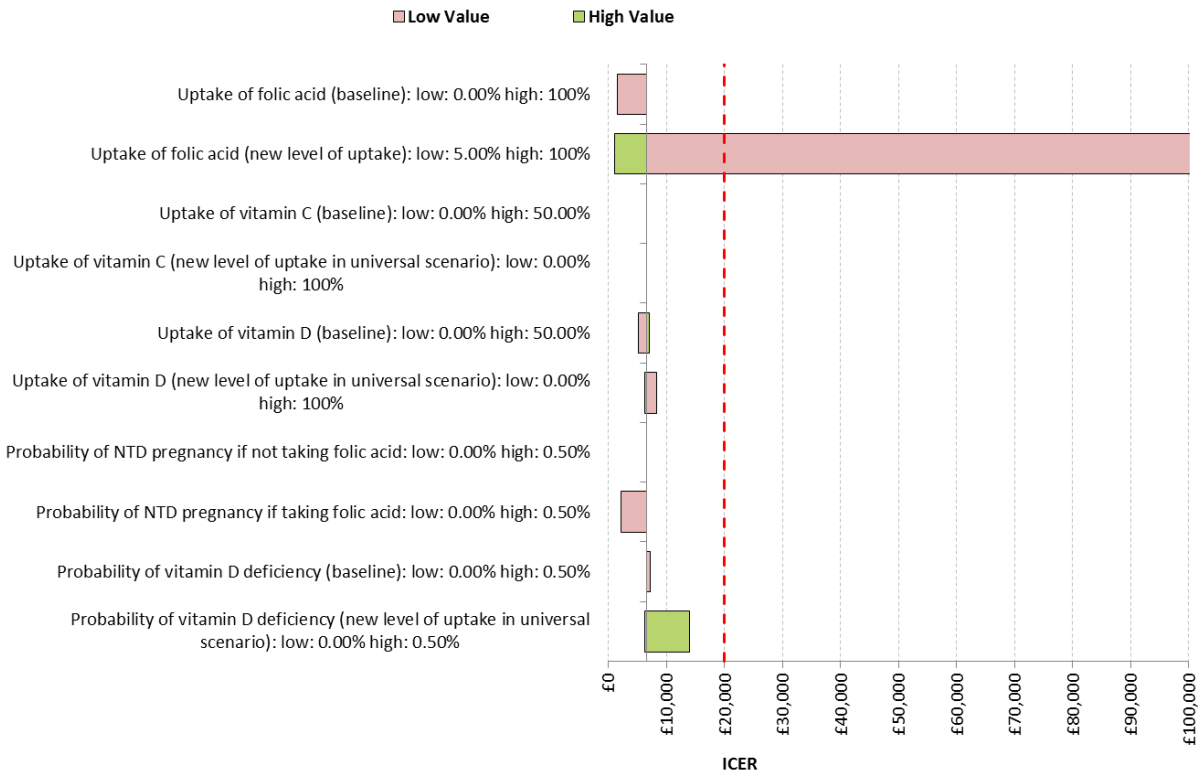
This tornado diagram shows that, for this subgroup, variation of most inputs does not change the direction of the results and the intervention is considered cost-effective. The biggest driver of change is the probability of vitamin D deficiency, if this was increased to the maximum value the ICER would increase over £20,000. However, it is important to note that, although it looks like a larger change, the ICER for the overall scheme (scenario 2) is actually altered by a similar amount to that in Graph 5.1 above. It appears to be a larger change on Graph 5.2 as it is being compared to other small changes, and therefore, the x-axis displays a different scale. The highest probability of vitamin D deficiency for the universal scenario does change the results to just over the £20,000 threshold meaning that the intervention may be considered not cost-effective at the high value.

**Graph 5.3: Infants and children over 6 months and under 4 years**



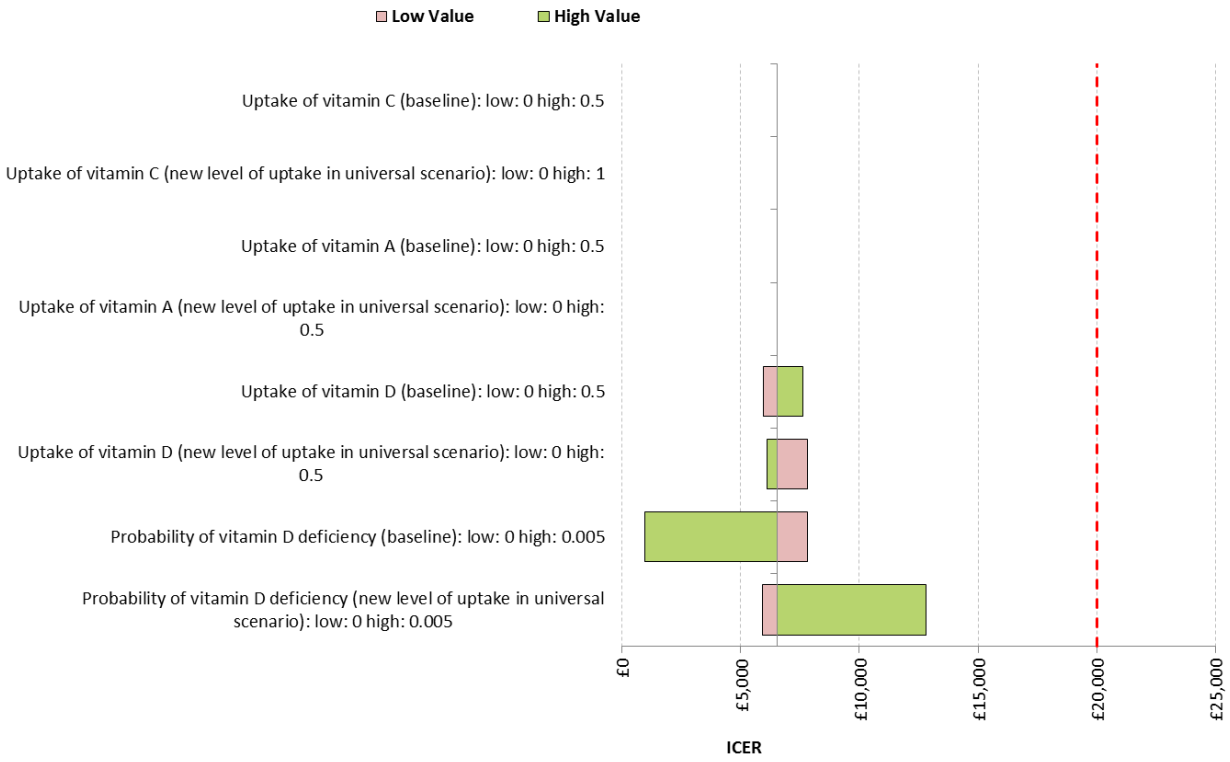

This graph shows that changing the uptake of vitamin C and vitamin A does not affect the cost-effectiveness of the overall scheme (scenario 2). This is because no benefits in terms of QALYs or cost-savings are quantified for vitamins C and A within the model. The biggest driver of cost-effectiveness in this subgroup is the probability of symptomatic vitamin D deficiency. Increasing or decreasing the uptake of vitamin D or the probability of symptomatic vitamin D deficiency can change the results over the £20,000 threshold meaning that the intervention may not be considered cost-effective. Threshold analyses show that the £20,000 threshold would be crossed when the probability of vitamin D deficiency (for the new level of uptake) is just under 0.2%.

**Graph 5.4: Women planning a pregnancy and up to 10 weeks**



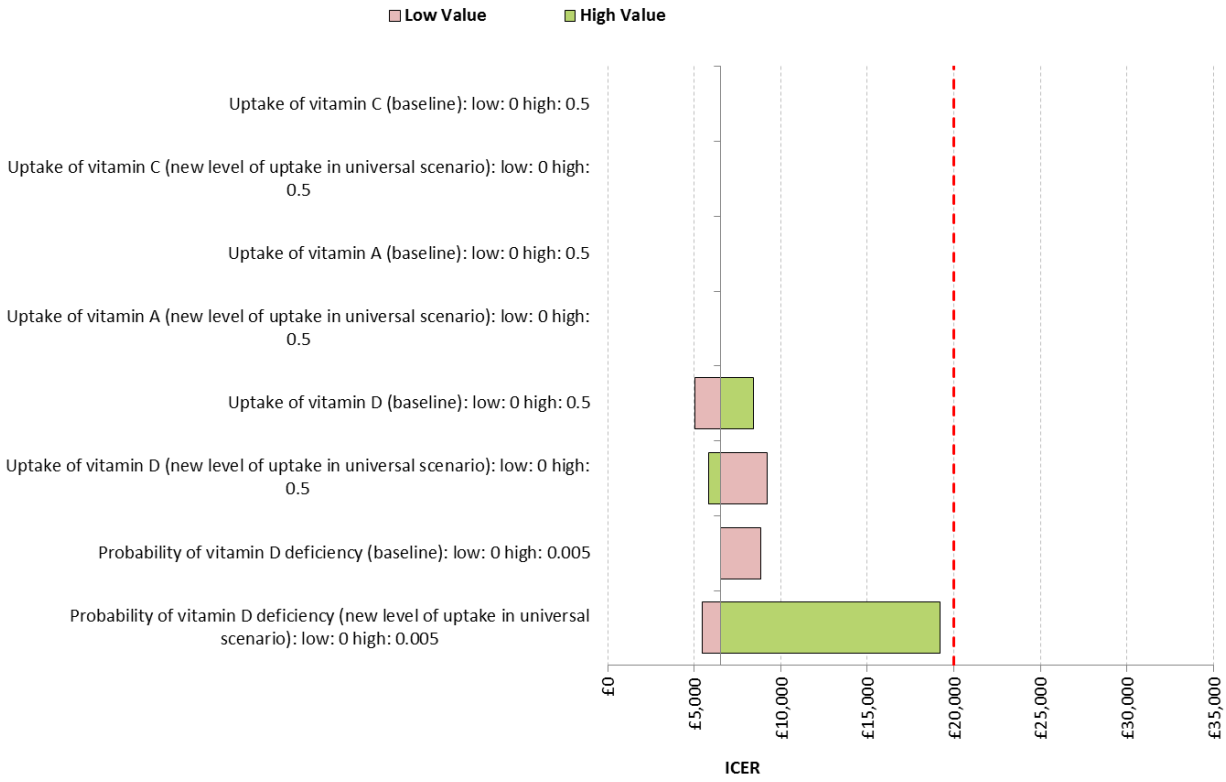

This graph illustrates that the uptake of folic acid is a key driver of cost-effectiveness of the overall scheme (scenario 2) and the only input when varied that causes the intervention not to be considered cost-effective is the uptake of folic acid in the new level of uptake. Threshold analyses show that the £20,000 threshold would be crossed when the new level of uptake of folic acid is under approximately 30%. The graph shows that the lower the level of uptake in the universal scenario, the higher the ICER will be. Similarly to Graph 5.1, the low value for the probability of pregnancies affected by a NTD if not taking folic acid and the high value for the probability of a pregnancy affected by a NTD if taking folic acid are not displayed as this results in universal supplementation being 'less effective'. If the probability of a pregnancy affected by a NTD when not taking folic acid is low there is little capacity to benefit, the intervention would result in extra costs for no benefit. When the probability of a pregnancy affected by a NTD when taking folic acid is high, this results in the intervention being 'less effective' as there is still a high probability of having a pregnancy affected by a NTD even when folic acid is taken, so there is no added benefit compared to not taking it.

**Graph 5.5: Infants aged 0 to 6 months**




The results in this graph are similar to those described in Graph 5.3 (children aged over 6 months and under 4 years) with the largest driver in this group being those inputs related to vitamin D. However, all changes shown on Graph 5.5 result in the intervention for the overall scheme (scenario 2) remaining cost-effective at a £20,000 threshold. This is due to this being a smaller population subgroup of the overall model population.

**Graph 5.6: Infants aged 4 to 5 years**




Similarly to Graphs 5.3 (children aged over 6 months and under 4 years) and 5.4 (children aged 0 to 6 months), the largest driver in this group are those inputs related to vitamin D. However, no variation of inputs causes the intervention for the overall scheme (scenario 2) not to be cost-effective.

### 5.2.1 Cost Sensitivity Analysis

The following sensitivity analyses vary the cost inputs used in the model. These univariate sensitivity analyses are run from the public perspective and include extending the offering universally to all current subgroups and all extended subgroups. The substitution coefficient is set at 0% meaning that all incremental Healthy Start uptake comes from new uptakers (as far as possible).

The blue line on each graph shows how the ICER changes when an input is varied. The dot on the line is the base case value (the value which is currently used in the model).

#### 5.2.1.1 Intervention costs

**Key messages from Cost of Extended Universal Scheme sensitivity analysis (on Scenario 2 results; Base Case ICER = £6,528):**

Set-up cost of universal scheme

- The ICER does not increase over £20,000 (cost-effectiveness threshold) even when fixed costs are as a high as approximately £14 million;
- Cost estimates from Lewisham for running the scheme in subsequent years generate an ICER of around £4,000.

Annual cost to run scheme per person

- The assumed annual cost of £[redacted] per person to run universal scheme (for local government) is cost-effective;
- This cost could be around £11.00 per person per year before crossing the £20,000 cost-effectiveness threshold, assuming that Lewisham's fixed costs apply.

Annual cost to DH per new Healthy Start vitamin supplementation application

- The cost per application can reach £ [redacted] before the ICER is over a £20,000 per QALY threshold.

Cost per vitamin coupon issued

When the cost is £[redacted] to issue each vitamin coupon the scheme is cost-effective;

- If this cost was just over £[redacted] then the intervention would no longer be cost-effective.

Price of vitamins

- When the price of women's and children's vitamins increases, the ICER increases;
- The price of children's vitamins is more sensitive than the price of women's vitamins.

**Graph 5.7: Set- up cost of universal scheme (local government) (fixed costs)**

NB Graph has been redacted here as it would be possible to work backwards to data submitted in confidence

Graph 5.7 shows the effect of varying the fixed costs (e.g. staff, advertising and licencing costs) in the first year of the universal scheme on the ICER. It shows that, the higher the fixed cost, the higher the ICER. The ICER does not increase over £20,000 even when the fixed costs are as high as approximately £14 million. When the cost is £0 the ICER is lowest. The cost estimates provided from Lewisham show that the fixed costs in subsequent years would be £[redacted], generating an ICER of around £4,000. These costs represent the annual costs of running the scheme, (e.g. licencing costs and distribution costs) that are incurred regardless of how many people use the scheme. This would represent the marginal cost-effectiveness of the scheme in subsequent years, when the set-up costs are not incurred and, therefore, the fixed costs per year are lower. Data from Birmingham suggest that fixed costs are very low as this scheme depends more on variable costs.

**Graph 5.8: Annual cost to run the scheme per person (local government) (variable costs) in the first year**

NB Graph has been redacted here as it would be possible to work backwards to data submitted in confidence

This graph shows how varying the cost of running the universal scheme (for local government) per person affects the ICER. This is an important sensitivity analysis because, due to a lack of data there is not an estimate of what the targeted scheme currently costs to run per person for local government. A conservative approach has been taken, whereby it has been assumed that this cost is £0 per person. Therefore, if indeed there is a cost per person of running the current scheme, the incremental cost between the two schemes would be reduced. Where the incremental cost per person per year reduces, the graph shows that it becomes increasingly cost-effective to move the scheme to a universal offering.

Further, this input is very uncertain as it is an estimate of cost from only two local government areas which provide very different values for variable costs per person in the first year (£[redacted] or £12.72). In subsequent years the cost per person is likely to be slightly lower (£[redacted] or £10.08). The cost could be around £11.00 per person per year before crossing the £20,000 threshold, assuming that Lewisham's fixed costs apply.

**Graph 5.9: Annual cost to DH per new Healthy Start vitamin supplementation application**

NB Graph has been redacted here as it would be possible to work backwards to data submitted in confidence

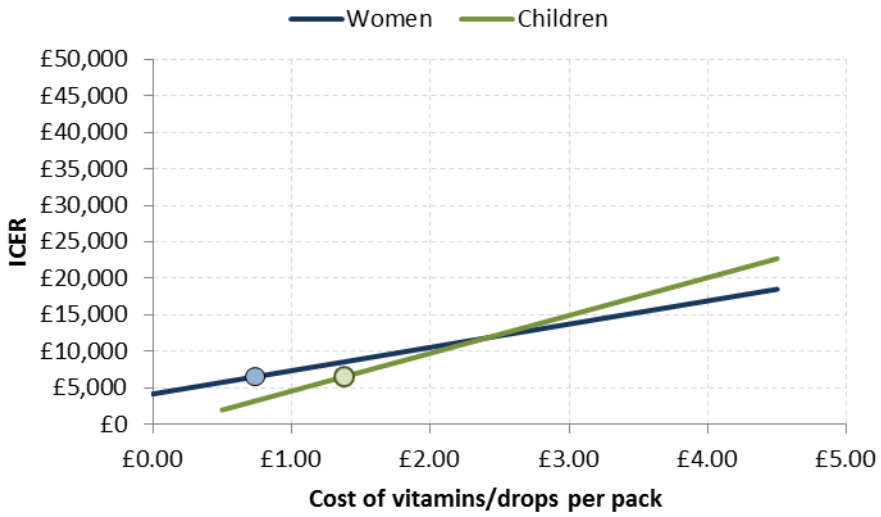
Graph 5.9 shows that as the cost per new application to join the scheme is increased, the ICER also increases. The cost per application would have to reach around £[redacted] before the ICER is over £20,000. This analysis assumes that application to the scheme is required. In reality, a universal scheme may be run in a different manner.

**Graph 5.10: Cost per vitamin coupon issued (DH)**

NB Graph has been redacted here as it would be possible to work backwards to data submitted in confidence

Graph 5.10 shows that the results are sensitive to varying the cost per vitamin coupon issued. The DH estimated that it would cost around £[redacted] to send out each vitamin coupon (when not issued with a food voucher in which case the cost is negligible); if this cost was increased to just over £[redacted] then the intervention would no longer be cost-effective. As it is not clear how vitamins would be distributed in a universal scheme, it is possible that coupons would no longer be issued, in which case there would be no cost for issuing coupons. However, other unknown costs may be incurred instead.

**Graph 5.11: Price of vitamins**




Graph 5.11 shows that, as expected, when the price of women's and children's vitamins increases, the ICER also increases. The graph shows that the price of the children's vitamins is more sensitive (it has a steeper curve). This is because the infants' and children's subgroups have a larger population than the women's subgroups and because the children's Healthy Start vitamin supplements have a higher price than the women's (i.e. they are more expensive and more are required). Although this is one of the more robust inputs in the model (this is the price currently charged for Healthy Start vitamin supplements), it is possible that moving to a universal scheme may change the price of the vitamins.

#### 5.2.1.2 Treatment costs

**Key messages from Treatment Cost Sensitivity Analysis (Scenario 2 results; Base Case ICER = £6,528):**

<u>Cost of symptomatic vitamin D deficiency</u>

- As the cost of treating symptomatic vitamin D deficiency increases, the ICER decreases;
- The universal intervention is cost-effective at all values considered.

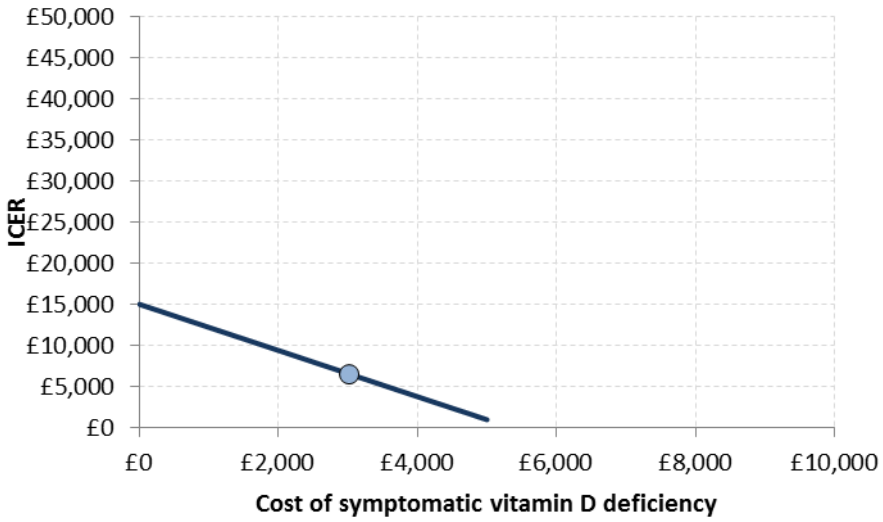
<u>Cost of lifetime treatment for NTD (to the public sector)</u>

- As the cost of lifetime treatment for NTD increases, the ICER decreases;
- The intervention is cost-effective at all values considered.

<u>Pregnancy affected by a NTD – proportion of terminations</u>

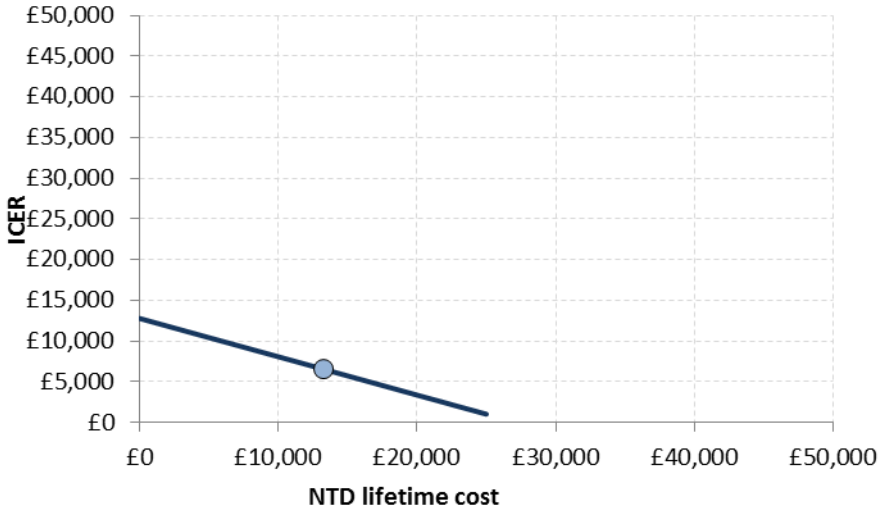
- As the proportion of terminations increases, the ICER increases;
- Where the proportion of terminations is above 92%, the intervention is no longer cost-effective at a £20,000 threshold.

**Graph 5.12: Cost of symptomatic vitamin D deficiency**



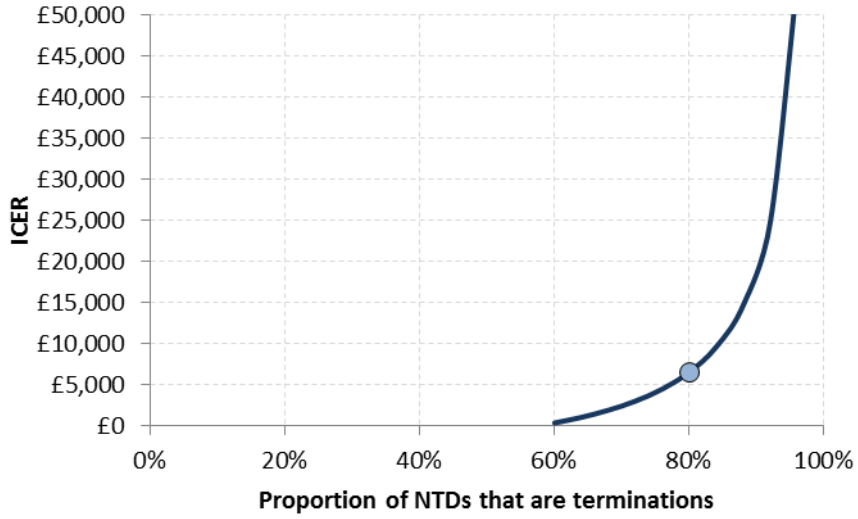

Graph 5.12 shows that, as the cost of treating symptomatic vitamin D deficiency increases, the ICER decreases. This is because the more that treating symptomatic vitamin D deficiency costs, the more can be saved by avoiding it.

**Graph 5.13: Cost of lifetime treatment for NTD (to the public sector)**




Graph 5.13 shows that, as the cost of lifetime treatment for NTDs increases, the ICER decreases. As above, this is because the higher the cost, the more potential savings can be made.

**Graph 5.14: Pregnancy affected by a NTD – number of terminations**




Graph 5.14 shows how the ICER would change if the proportion of pregnancies affected by a NTD that result in termination is varied. It shows that, as the proportion of terminations increases, the ICER also increases. As the proportion of pregnancies affected by a NTD resulting in termination is increased, the proportion of NTD births is decreased. This means that the number of people incurring the average cost of treating someone with NTD over their lifetime is reduced and there is less capacity to benefit. Where the proportion of terminations is above 92%, the intervention is no longer cost-effective at a £20,000 threshold.

## 5.3 SCENARIO ANALYSIS

### 5.3.1 NHS Perspective

**Key messages of results from NHS perspective:**

- Scenario 1: The ICER is 'dominant' (lower or equal costs and increased effectiveness) from the NHS perspective;
- Scenario 2: Extension on a universal basis to the current and extended subgroups generates a 'dominant' ICER from the NHS perspective.

**Table 5.4: Results from NHS perspective – universal offer extended to current subgroups (Scenario 1)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £0 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £0 |
| Cost of intervention (set up) | £0 | £0 | £0 |
| Cost of treatment (NTDs, vitamin D deficiency) | £30,758,128 | £26,372,547 | -£4,406,434 |
| **Total incremental cost** | | | **-£4,406,434** |
| QALYs lost (pregnancy affected by a NTD) | 3,635 | 3,623 | -13 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **13** |
| **ICER** | | | **Dominant** |

* The incremental cost only was calculated.

Table 5.4 shows the model results from the NHS costs perspective when the offer is extended on a universal basis to the current subgroups, only. This option has an extremely high ICER from the public sector perspective but from the NHS perspective the ICER is 'dominant' (this means that there are lower (or equal) costs and increased effectiveness). The reason for this being that local government and central government pay most if not all the costs of the scheme, but the NHS benefits because its treatment costs fall with supplementation.

**Table 5.5: Result from NHS perspective – universal offer extended to current subgroups and all extended subgroups (Scenario 2)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £0 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £0 |
| Cost of intervention (set up) | £0 | £0 | £0 |
| Cost of treatment (NTDs, vitamin D deficiency) | £54,730,291 | £43,695,433 | -£11,065,538 |
| **Total incremental cost** | | | **-£11,065,538** |
| QALYs lost (pregnancy affected by a NTD) | 6,870 | 6,120 | -750 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **750** |
| **ICER** | | | **Dominant** |

* The incremental cost only was calculated.

Table 5.5 shows that the ICER is also dominant when the scheme is extended to all the current and extended subgroups on a universal basis. The reasons for this are explained above. The cost savings are even higher when the scheme is rolled out to more people, as the NHS does not incur the costs, while the more people that take supplements, the less people will need NHS funded treatment.

It is not clear if there may be some small costs to the NHS. However, it is unlikely that these costs would be as high as they are for the public sector (which includes costs to the DH and local government).

### 5.3.2 Societal Perspective

**Key message of results from Societal perspective:**

- Scenario 2: Extension on a universal basis to the current and extended subgroups generates a 'dominant' ICER from the societal perspective;
- This assumes a 50% substitution coefficient. Interpreting this coefficient is difficult, a full description is provided in Appendix B.

Primary data collection was undertaken to identify inputs for the societal perspective, as discussed in Section 3.1.2.

#### 5.3.2.1 Primary data collection results

Table 5.6 summarises the results of the primary data collection survey.

**Table 5.6: Primary data collection summary**

| Survey group | Proportion of total sample taking vitamins | Proportion of total sample buying vitamins* | Proportion of total sample (by group) paying privately | Average price paid** |
|---|---|---|---|---|
| Women planning | 73% (said they take supplements) | 91% (said they buy vitamins for themselves) | 68.89% | £7.02 per pack / £0.11 per dose / £40.28 annual cost |
| Pregnant women | 80% (said they take supplements) | 93% (said they buy vitamins for themselves) | 70.75% | £8.41 per pack / £0.15 per dose / £56.42 annual cost |
| Women with children aged 0 to 5 years - children | 37% (said their children take supplements) | 61% (said they buy vitamins for their children) | 49.63% | £7.42 per pack / £0.18 per dose / £66.77 annual cost |
| Women with children aged 0 to 5 years | 66% (of women with a child under 12 months said they take vitamins) | N/A | 55.79% | £6.64 per pack / £0.12 per dose / £43.80 annual cost |

* Difference exists due to tablets being purchased, but not taken.

** Within the model, the average annual cost was determined by multiplying the proportion of total sample paying privately by the average price paid.

There is some concern that the results are not representative of the general population. The survey sample was a general population sample of respondents that were signed up to survey panels. The relevant population groups were targeted on these panels. The proportion of the survey sample that report that they are buying and taking vitamins is higher than expected, as is the price paid for the vitamins. The results in the primary data collection are not similar to the results reported in the national surveys.

Further analysis showed that there were a higher proportion of people receiving some kind of state benefit than would be expected in the general population. The survey asked if the respondent was in receipt of any of the following:

**a)** Income-based jobseeker's allowance;
**b)** Income-related employment and support allowance;
**c)** Income support;
**d)** Working tax credits;
**e)** Working tax credit run-on;
**f)** Child tax credit **and** with an annual family income of over £16,190;
**g)** Child tax credit **and** with an annual family income of £16,190 or less;
**h)** Housing benefit;
**i)** Universal credit.

The number of people reporting that they were receiving benefits was as follows: 51.67% of women planning a pregnancy; 45.58% of pregnant women and 70.37% of women with children up to five years old. National data from the Department of Work and Pensions reports (34) that there were 5.3 million working age benefit claimants in 2014 (which equates to approximately 8.11% of the UK population). As previous surveys have shown, those in a lower income bracket tend to be less likely to take vitamin supplements and be those most at risk, making the findings of this survey counterintuitive.

#### 5.3.2.2 Approach taken to societal perspective

Due to the survey sample being unrepresentative and due to the information gathered in the survey not being consistent with the national surveys, there were some concerns about applying the primary data collection data in the economic model (which uses national survey uptake and effectiveness inputs).

The approach taken was to apply the cost that respondents reported paying, adjusted for the proportion of the population that reported paying privately. Due to concerns about the uptake data from the survey being unrepresentative, it was agreed with the ERG this would not be used in the model. Instead data previously used in the model from the national surveys were used. However, in the absence of any other data regarding the prices paid for vitamins, data from the primary data collection survey were used. The analysis is limited by the use of two data sources. Table 5.7 illustrates the results when applying the societal perspective. However, the results of this table should be read as an illustrative example, bearing in mind all of the uncertainties in the model and the limitations of the primary data collection survey.

The results are reported with a 50% substitution coefficient as the results of the societal perspective are dependent on the proportion of the population that substitute. Some of the people that previously purchased the vitamins would receive the vitamins free in the universal scenario.

**Table 5.7: Results from a societal perspective – universal offer extended to all current subgroups plus all extended subgroups – 50% substitution coefficient (Scenario 2)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £7,136,203 |
| Private purchase cost of vitamins | £188,520,435 | £173,798,802 | -£14,721,634 |
| Cost of intervention (distribution) | NA* | NA* | £6,148,818 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £92,405,633 | £83,445,366 | -£8,931,513 |
| **Total incremental cost** | | | **-£7,693,701** |
| QALYs lost (pregnancy affected by a NTD) | 6,870 | 6,599 | -270 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **270** |
| **ICER** | | | **Dominant** |

* The incremental cost only was calculated.

The table shows that when the societal perspective is taken, the ICER is dominant (extra benefits for less, or equal, cost). The societal perspective will always improve the ICER as the price paid for vitamins reported in the primary data collection survey is very much higher than the cost of Healthy Start vitamin supplements. Applying the societal perspective means that for those people who substitute, they will have the same health benefits for lower cost. Further, the cost of a pregnancy affected by a NTD is higher in the societal perspective, as it includes lost productivity to the caregiver and increased sick days to the person with spina bifida, therefore, more savings can be made by avoiding pregnancies affected by a NTD (26).

### 5.3.3 Discount Rate

**Key Messages from the Scenario Analysis of Discount Rate:**

- As the discount rate decreases, the ICER decreases;
- The ICER for Scenario 2 is lowered to £1,885 when the discount rate is lowered to 1.5%.

The model is run with a discount rate for costs and benefits of 3.5% per year. In the past, economic models of public health interventions have often used a discount rate of 1.5%. Table 5.8 below, shows the results when the model is run with a discount rate of 1.5% when extending the universal offering to all current subgroups and extended subgroups from the societal perspective.

Table 5.8 shows that, as the discount rate is lowered the ICER is also lowered. In order to allow easy comparability, the incremental column of the results table when the model is run with a 3.5% discount rate is shown in the table. Compared to the results when run with a discount rate of 3.5%, the ICER is much lower. This is due to the lifetime cost and benefits of spina bifida being included in the model. Because these have a long time horizon, discounting at a lower rate increases the present value of costs and benefits incurred further into the future. The table shows that the differences in costs result from differences in the treatment costs (which includes spina bifida) and in the QALYs lost from pregnancies affected by a NTD.

**Table 5.8: Results - discounting at 1.5% and 3.5% (Scenario 2)**

| Discounted at 1.5% | | | | Discounted at 3.5% |
|---|---|---|---|---|
| **Summary table** | **Targeted** | **Universal** | **Incremental** | **Incremental** |
| Cost of HS vitamins | NA* | NA* | £7,136,203 | £7,136,203 |
| Private purchase cost of vitamins | £0 | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £6,148,818 | £6,148,818 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £78,695,674 | £65,021,001 | -£13,674,672 | -£11,065,538 |
| **Total incremental cost** | | | **£2,284,773** | **£4,893,907** |
| QALYs lost (pregnancy affected by a NTD) | **11,284** | **10,053** | **-1,231** | **-750** |
| **Total QALYs gained** | | | **1,230** | **750** |
| **ICER** | | | **£1,855** | **£6,528** |

* The incremental cost only was calculated.

### 5.3.4 Scenario Analysis of Adding QOL Benefits to Vitamin D

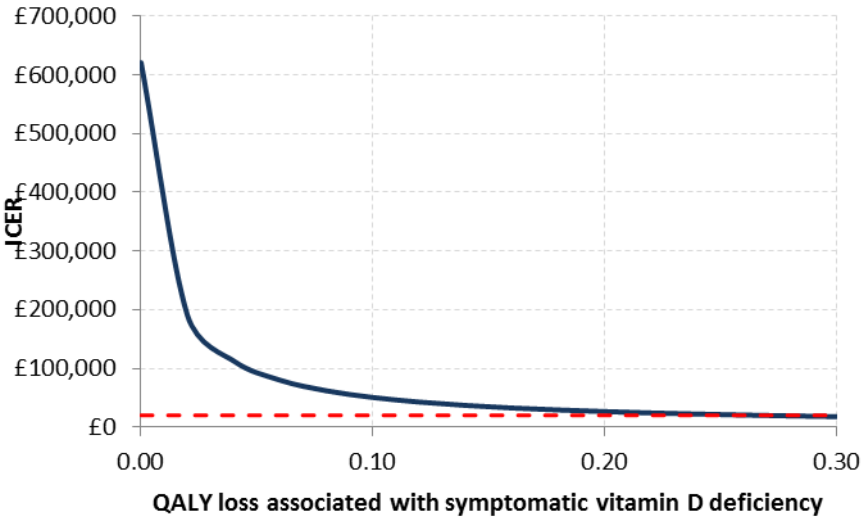
**Key messages from the scenario analysis of Adding QOL Benefits to Vitamin D:**

- Applying a QALY loss for people that have symptomatic vitamin D deficiency reduces the ICER in scenario 1 and 2.
- In scenario 1, when the QALY loss associated with symptomatic vitamin D deficiency is above approximately 0.27 then the ICER will be below £20,000.

An exploratory sensitivity analysis to model the effects of assigning QOL benefits to vitamin D has been carried out, in the absence of any data to indicate what the QALY loss might be. The QOL is applied to those with symptomatic vitamin D deficiency, not the whole population. The ERG felt that it was not plausible that there would be a significant impact on QOL from vitamin A and C deficiency. Therefore, QOL benefits for vitamins A and C were assumed to be zero in this analysis. A recent systematic review (35) with the aim of reviewing the literature regarding QOL outcomes from vitamin D supplementation concluded that most articles reviewed were of poor methodological quality and that vitamin D supplementation was not associated with significant changes in QOL. However, vitamin D supplementation may have a small to moderate effect on QOL when used on a short-term basis in a diseased population. Although the review states that supplements do not provide a significant improvement in quality of life, this is almost certainly because a huge proportion of those people receiving supplements would not have symptomatic deficiency anyway. The disutility applied in the model is specifically for those people that do have symptoms.

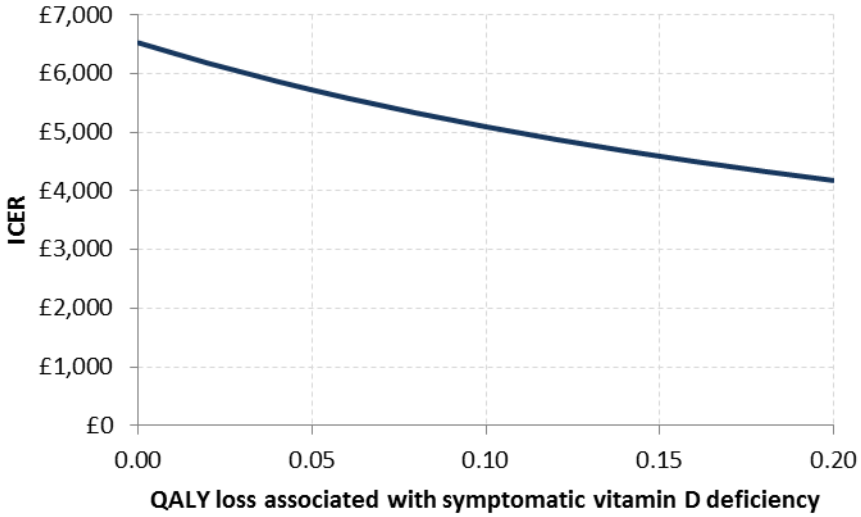
One-way sensitivity analyses have been carried out which illustrate the threshold at which the QALY loss associated with symptomatic vitamin D deficiency would be to cross the cost-effectiveness threshold.

**Graph 5.15: QALY loss associated with symptomatic vitamin D deficiency – Scenario 1**




Graph 5.15 illustrates that, in scenario 1, when the QALY loss associated with symptomatic vitamin D deficiency increases, the scheme is more likely to be cost-effective. If a QALY loss of 0.1 is assumed, the scheme would still not be cost-effective, with an ICER of £50,513. This threshold analysis shows that if the QALY loss associated with symptomatic vitamin D deficiency is above approximately 0.27 then the ICER will be below the £20,000 threshold shown on the graph.

**Graph 5.16: QALY loss associated with symptomatic vitamin D deficiency – Scenario 2**




Graph 5.16 shows that including QALY loss associated with symptomatic vitamin D deficiency results in a lower ICER in scenario 2.

### 5.3.5 Consideration of Over Supplementation

The ERG members queried the possibility of unintended effects through over supplementation but were aware this issue has been considered by the Committee on Toxicology. Therefore, this was not modelled as part of this analysis. This issue is considered further in the report to the CMO.

### 5.3.6 Prescription Charges

**Key messages from Prescription Charges (Scenario 2):**

- From a public sector perspective when Healthy Start supplements are provided universally in the current and extended subgroups, including prescription charges improves cost-effectiveness. However, the ICER of £30,855 is still not cost-effective at a £20,000 threshold;
- From a societal perspective when Healthy Start supplements are provided universally in the current and extended subgroups including prescription charges results in a 'dominant' ICER.

Prescription charges to the CCG and to the person paying for the prescription have been included as a scenario analysis. This is not included in the base case model inputs as there is too much uncertainty surrounding the inputs. The actual cost for a prescription charge in Birmingham CCGs was obtained. A weighted average was calculated, resulting in a cost per prescription to the CCG of £2.09. The cost to the person paying for a prescription is £8.05. This cost was only applied to women planning pregnancy because pregnant women, women 12 months post-partum and children are eligible for free prescriptions.

There is little information available about the number of people that receive prescriptions for vitamins currently. The IFS reports that between 15% and 30% of mothers that give vitamin supplements to their babies aged 4 weeks to 10 months get vitamin supplements on prescription, with the proportion decreasing as the infant's age increases. However, this is not enough information to populate the inputs for all subgroups. Further, there is no information about how the proportion might change if the Healthy Start vitamin scheme moved to a universal offering.

The approach taken to model this scenario used the number of people substituting vitamins obtained on prescription or purchased privately for Healthy Start vitamin supplements. The substitute coefficient was set at 50%. Then, a proportion of those substitutes are assumed to have previously received a prescription, the rest of the substitutes are assumed to have previously paid privately for vitamins. The proportion of substitutes that previously received prescriptions was set at 22.5% for women and babies (the mid–point of the proportions given in the IFS).

Results are reported below for all current and extended subgroups from the public sector and societal perspectives.

**Table 5.9: Results from public sector perspective (Scenario 2)**

| **Summary table** | **Targeted** | **Universal** | **Incremental** |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £7,136,203 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| CCG cost of prescriptions | NA* | NA* | -£166,735 |
| Private cost of prescriptions | NA* | NA* | £0 |
| Cost of intervention (distribution) | NA* | NA* | £6,148,818 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £54,786,787 | £47,355,778 | -£7,451,009 |
| **Total incremental cost** | | | **£8,341,702** |
| QALYs lost (pregnancy affected by a NTD) | 6,870 | 6,599 | -270 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **270** |
| **ICER** | | | £30,855 |

* The incremental cost only was calculated.

Including prescription charges in the public sector perspective, results in additional savings to the CCG through not having to provide prescriptions, thereby making the intervention more cost-effective. This accounts for people who now take Healthy Start vitamin supplements who previously obtained their vitamins by prescription.

**Table 5.10: Results from societal perspective (Scenario 2)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £7,136,203 |
| Private purchase cost of vitamins | £188,520,435 | £177,111,169 | -£11,409,266 |
| CCG cost of prescriptions | NA* | NA* | -£166,735 |
| Private cost of prescriptions | NA* | NA* | -£47,297 |
| Cost of intervention (distribution) | NA* | NA* | £6,148,818 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £92,405,633 | £83,474,120 | -£8,931,513 |
| **Total incremental cost** | | | **-£4,595,365** |
| QALYs lost (pregnancy affected by a NTD) | 6,870 | 6,599 | -270 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **270** |
| **ICER** | | | **Dominant** |

* The incremental cost only was calculated.

Including prescription charges in the societal perspective, results in an additional saving to CCGs through not having to provide prescriptions. It also results in a saving in the private cost of prescriptions. This accounts for those women planning a pregnancy who previously may have obtained their vitamin supplements by paid prescription but substitute with Healthy Start vitamin supplements in a universal scenario.

### 5.3.7 QALY Loss for Unborn Children

**Key message from QALY Loss for Unborn Children:**

- The model shows that including lifetime QALYs for termination and babies born with anencephaly is cost-effective with an ICER of £582 for Scenario 2.

The ERG requested that the life lost for births that are terminated in the model be accounted for in a scenario analysis. Lifetime QALYs were assigned to each case of NTD avoided in the model. This accounts for the difference between a normal healthy life expectancy and the consequences of each case of NTD, accounting for both terminations and each baby born with anencephaly (lifetime QALY calculations are described in Section 4.5.1). Table 5.11 shows the results for all current and extended subgroups from the public sector perspective.

**Table 5.11: Results including lifetime QALYs for terminations (Scenario 2)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £7,136,203 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £6,148,818 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £54,786,787 | £43,721,249 | -£11,065,538 |
| **Total incremental cost** | | | **£4,893,907** |
| QALYs lost (pregnancy affected by a NTD) | 77,000 | 68,597 | -8,403 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **8,403** |
| **ICER** | | | **£582** |

* The incremental cost only was calculated.

As expected, adding lifetime QALYs for termination and babies born with anencephaly results in a much lower ICER. This is because the costs remain the same but there are many more QALYs saved from preventing pregnancies affected by a NTD.

### 5.3.8 Consideration of Born in Bradford Data

**Key message from Consideration of Born in Bradford Data:**

- The use of the Born in Bradford data results in a slightly lower ICER of £4,910 for Scenario 2, compared with a base case ICER of £6,528.

The Born in Bradford (BiB) study is a long term study of 13,857 children born at Bradford Royal Infirmary between April 2007 and June 2011[7]. The study collected information about pregnant mothers' vitamin supplement use. The relevant information to this project asked if mothers took vitamin D supplements, vitamin C supplements, Sanatogen or Pregnacare. These data were not used in the base case as the national surveys (IFS, NDNS, DNSIYC) have a larger sample size and report supplement use in more detail and for more population groups. However, the BiB data has been used in a scenario analysis as the cohort is 60% Black and Minority Ethnic Groups (BMEG) groups, which allows a useful comparison with IFS were the proportion of BMEG participants is lower.

Analysis of the Born in Bradford data showed that in 15.48% of pregnancies, women took a supplement containing vitamin D and in 15.37% of pregnancies, women took a supplement containing vitamin C (both of which report lower uptake than the national survey data currently used in the model). No information is provided about when in the pregnancy women took the vitamin supplements. Therefore, within this scenario in the model this was applied to the baseline uptake for those women who were pregnant before 10 weeks and those who were pregnant after 10 weeks. Table 5.12 shows the results for all current and extended subgroups from the public sector perspective when the BiB data are used.

[7] http://www.borninbradford.nhs.uk/about-the-project/

**Table 5.12: Results using BiB data (Scenario 2)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £7,136,203 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £6,148,818 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £56,837,488 | £44,558,618 | -£12,287,870 |
| **Total incremental cost** | | | **£3,680,576** |
| QALYs lost (pregnancy affected by a NTD) | 6,870 | 6,120 | -750 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **750** |
| **ICER** | | | **£4,910** |

* The incremental cost only was calculated.

The results table shows that the ICER is slightly lower than when the base case values are used. The reason that the ICER is lower is that there are more costs saved from treating vitamin D deficiency. The costs saved from preventing pregnancies affected by a NTD does not change from the base case, as the incremental number of people taking vitamin supplements remains the same. However, the vitamin D costs do change because, as explained in Section 4.3.4, the vitamin D effectiveness inputs use the levels of uptake to calculate the number of people with vitamin D deficiency. As an exponential function is applied, if the baseline uptake is lower there will be more of a reduction in symptomatic vitamin D deficiency. This is because the curve is steeper at first meaning that more benefit is gained for the first people to take supplements.

### 5.3.9 Scenario analysis of Bestwick *et al.* (2014) (18) folic acid uptake data

**Key message from Scenario Analysis – Bestwick *et al.* (Scenario 2):**

- Using data from Bestwick *et al.* to populate the baseline uptake of folic acid supplements in women planning a pregnancy has a minimal impact on the ICER.

Bestwick *et al.* (18) report the uptake of folic acid for women. This was based on a survey of 466,860 women planning a pregnancy who had attended an antenatal screening clinic in London between 1999 and 2012.

The paper reports that in 2011-12, 28% (adjusted figure[8]) of women planning pregnancy took folic acid supplements. The IFS reported that 37% of mothers said that they took folic acid supplements when they were planning a pregnancy (this is the number used in the base case). The Bestwick paper is based on a larger sample than the IFS and is based on a sample of pregnant women, rather than new mothers. However, it is not a nationally representative sample.

[8] Adjusted for maternal age, maternal weight, ethnicity, previous pregnancy affected by a NTD, previous Down's syndrome pregnancy, IVF, diabetes, smoking, Down's syndrome screening test and region of England.

As reported in the base case results for scenario 2 (Section 5.1.3) the ICER is £6,528. Results are not reported in this scenario analysis for scenario 1 as this scenario does not include the subgroup of women planning pregnancy. The impact of using the Bestwick *et al.* data is minimal, resulting in a slightly lower ICER of £6,401.

### 5.3.10 Source of uptake – New users versus substitution

**Key message from Source of Uptake – New Users Versus Substitution (Scenario 2):**

- Interpretation of the substitution coefficient is difficult as the relationship is non-linear. Appendix B provides a full description of the coefficient;
- Where the substitution coefficient is 100%, all additional Healthy Start uptake is from substitutes as far as possible. The ICER is infinite (extra cost with no additional health benefits);
- Where the substitution coefficient is 50%, uptake is split proportionally between substitutes and new uptakes. The ICER is £31,472 and is not cost-effective in a £20,000 threshold;
- The overall results are highly sensitive to variations in the substitution coefficient.

As described in Section 4.2.2 the model includes a substitution coefficient that can be used to calculate different uptake scenarios. As explained in Section 4.2.2, the substitution coefficient determines the breakdown of the increase in Healthy Start vitamin supplements between the proportion that are new 'uptakers' (they did not take any supplements before) and the proportion that are substituting (they previously paid for their supplements but now they get them free).

The results reported in the base case include a substitution coefficient of 0% which assumes that all additional Healthy Start uptake is from people who were not previously taking vitamin supplements. When the substitution coefficient is 100%, this means that all additional Healthy Start uptake is from substitutes (except when the baseline uptake is too low). When the substitution coefficient is 50% it assumes that Healthy Start vitamin supplements uptake is proportionally split between new uptake and substitutes. More detail is given in Section 4.2.2 or the technical appendix (Appendix B).

The following sections report the results when Healthy Start vitamin supplements are offered universally to the current and extended subgroups when the substitution coefficient is 100% and 50% from the public sector perspective (a substitution coefficient of 0% is used in the base case results reported above).

### 5.3.11 Substitution Coefficient 100% - Maximum Substitution, All Healthy Start Uptake is from Substitutes

When the substitution coefficient is 100% this means that the entire additional Healthy Start uptake comes from those already taking supplements (for which they have privately paid for or got on prescription). In this scenario, Healthy Start vitamin supplement uptake is from people substituting the vitamins they previously took with Healthy Start vitamin supplements, with no additional uptake of vitamins overall. However, if the uptake of Healthy Start vitamin supplements is higher than the baseline uptake, then some additional uptake will be added on as it cannot all come from substitutes. Table 5.13 shows the results when the substitution coefficient is 100%

**Table 5.13: Results when substitution coefficient 100% (Scenario 2)**

| **Summary table** | **Targeted** | **Universal** | **Incremental** |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £7,136,203 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £6,148,818 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £56,786,787 | £51,692,046 | -£3,094,741 |
| **Total incremental cost** | | | **£12,864,705** |
| QALYs lost (pregnancy affected by a NTD) | 6,870 | 6,870 | 0 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **0** |
| ICER | | | Infinite** |

* The incremental cost only was calculated;
****** There is an incremental cost for no additional benefit.

The results table shows that there is equal efficacy because all uptake is substituted. So although more Healthy Start vitamin supplements are taken, there are no extra health benefits because these people were already taking vitamin supplements.

### 5.3.12 Substitution Coefficient 50% - Healthy Start Uptake is Split Proportionally between New Uptake and Substitutes

The substitution coefficient in this scenario is 50%. In this scenario it is assumed that the Healthy Start uptake is split proportionally between new uptake and substituted uptake. The proportion depends on the baseline uptake.

**Table 5.14: Results when substitution coefficient is 50% (Scenario 2)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £7,136,203 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £6,148,818 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £56,786,787 | £47,335,778 | -£7,451,009 |
| **Total incremental cost** | | | **£8,508,437** |
| QALYs lost (pregnancy affected by a NTD) | 6,870 | 6,599 | -270 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **270** |
| **ICER** | | | £31,472 |

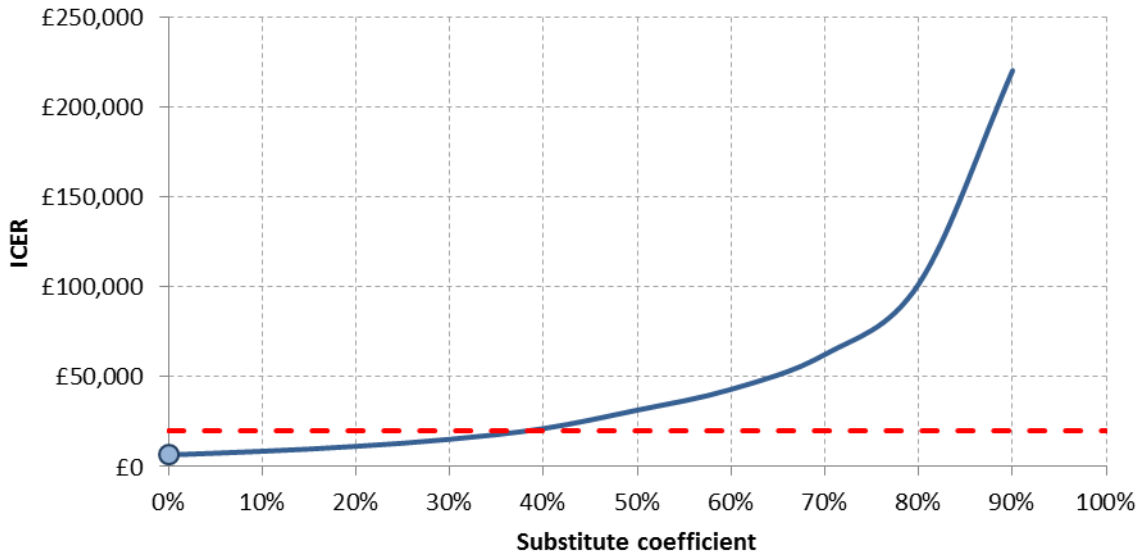
* The incremental cost only was calculated.

The results table shows that when the substitution coefficient is 50%, there are still not enough new people taking vitamins for the intervention to be cost-effective.

### 5.3.13 Substitution Coefficient Sensitivity Analysis

The scenarios above show that when the substitution coefficient is 100% and 50% moving the Healthy Start scheme to a universal scheme for all the current subgroups and extended subgroups is not cost-effective. Univariate sensitivity analysis was carried out in order to test how sensitive the substitution coefficient is to the cost-effectiveness.

**Graph 5.17: Sensitivity analysis of substitution coefficient (Scenario 2)**




Graph 5.17 shows that the results are very sensitive to the substitution coefficient. Moving Healthy Start to a universal scenario is only cost-effective when the coefficient is below around 40%. When the coefficient is below 40% this suggests that the majority of the Healthy Start uptake must come from new uptake, rather than substitutes. Interpretation of the coefficient is very difficult given that the uptake relationship is not always linear (this is fully described in technical Appendix B).

Table 5.15 shows what an uptake coefficient of 40% translates to in terms of the additional uptake for each subgroup. This table is based on the base case inputs in the model and the reader should note that the baseline uptake is different for each vitamin and subgroup, meaning that the coefficient has a different impact for each vitamin and subgroup.

**Table 5.15: Increase in uptake for a substitution coefficient of 40%**

| | Folic acid | Vitamin A | Vitamin C | Vitamin D |
|---|---|---|---|---|
| Pregnant women after 10 weeks | 16.32% | NA | 13.76% | 13.24% |
| Women with a child up to 12 months | 14.11% | NA | 14.11% | 14.11% |
| Infants and children over 6 months and under 4 years | NA | 15.9% | 15.9% | 15.9% |
| Women planning a pregnancy | 14.1% | NA | 16.3% | 16.3% |
| Pregnant women before 10 weeks | 7.4% | NA | 13.8% | 13.2% |
| Infants aged 0 to 6 months | NA | 15.9% | 15.9% | 15.9% |
| Infants and children over 4 years and under 5 years | NA | 15.4% | 15.4% | 15.5% |

## 5.4 TWO-WAY SENSITIVITY ANALYSIS

**Key messages from Two-Way Sensitivity Analysis of Healthy Start Uptake and Substitution Coefficient (Scenario 2):**

- Women: the ICER is highly sensitive to both the substitution coefficient and uptake of Healthy Start vitamin supplements;
- Children: the ICER is sensitive to uptake. As uptake increases, the ICER increases. This is because the higher the uptake is for children, the higher the costs of supplementation are, without any benefits to QOL.

Two-way sensitivity analysis allows for two input parameters to be varied at one time.

Table 5.16 and 5.17 show the model results when the Healthy Start substitution coefficient is varied between 0% (all Healthy Start uptake is from new uptakers) and 100% (all Healthy Start uptake is from substitutes). The second parameter that is varied is the change in Healthy Start uptake. The ERG requested that the model reports the minimum uptake required in order for the results to be cost-effective. As the report has set out, there is a lot of uncertainty in the model and the results presented depend on these uncertain input parameters. However, the model results are extremely sensitive to varying the substitution coefficient. Each table shows ICERs over £30,000 in red (unlikely to be considered cost-effective), ICERs between £20,000 and £30,000 in orange (may be considered cost-effective) and those under £20,000 in green (likely to be considered cost-effective).

**Table 5.16: Healthy Start uptake and substitution coefficient – Women**

| | | Change in HS uptake - women | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
| Substitute coefficient | 0% | Equal efficacy | £15,717 | £6,528 | £5,969 | £5,953 | £5,998 | £6,073 | £7,034 | £8,374 | £9,718 | £11,062 |
| | 10% | Equal efficacy | £19,068 | £8,487 | £6,445 | £6,483 | £6,572 | £6,679 | £7,037 | £8,374 | £9,718 | £11,062 |
| | 20% | Equal efficacy | £23,576 | £11,126 | £7,143 | £7,064 | £7,205 | £7,357 | £7,505 | £8,376 | £9,718 | £11,062 |
| | 30% | Equal efficacy | £29,960 | £14,869 | £10,019 | £7,703 | £7,908 | £8,113 | £8,308 | £8,492 | £9,718 | £11,062 |
| | 40% | Equal efficacy | £39,694 | £20,582 | £14,412 | £11,436 | £9,713 | £8,962 | £9,215 | £9,448 | £9,720 | £11,062 |
| | 50% | Equal efficacy | £56,343 | £30,364 | £21,939 | £17,858 | £15,487 | £13,956 | £12,893 | £12,116 | £11,526 | £11,062 |
| | 60% | Equal efficacy | £72,824 | £40,160 | £29,439 | £23,635 | £19,425 | £16,884 | £15,204 | £13,919 | £12,260 | £11,062 |
| | 70% | Equal efficacy | £100,359 | £56,591 | £42,039 | £32,887 | £25,056 | £20,789 | £18,144 | £16,111 | £13,057 | £11,062 |
| | 80% | Equal efficacy | £155,535 | £89,630 | £67,420 | £49,978 | £33,746 | £26,247 | £22,005 | £18,835 | £13,926 | £11,062 |
| | 90% | Equal efficacy | £321,287 | £189,147 | £143,981 | £91,707 | £48,853 | £34,405 | £27,300 | £22,308 | £14,877 | £11,062 |
| | 100% | Equal efficacy | Equal efficacy | Equal efficacy | Equal efficacy | £341,160 | £81,432 | £47,895 | £35,004 | £26,889 | £15,920 | £11,062 |

Table 5.16 shows that, with a 0% substitution coefficient (maximum new uptakers), the ICER falls, the greater the increase in Healthy Start uptake. This is true up to 40% Healthy Start uptake, at which point the ICER starts to increase. The reason that the ICER starts to increase as the change in Healthy Start uptake increases is that at a higher Healthy Start uptake there is no longer any capacity to benefit in some cases. For example, the uptake of folic acid in pregnant women before 10 weeks is already 79%, so an increase in Healthy Start uptake of 60% (when the substitution coefficient is 0%, meaning all Healthy Start uptake is new uptake) only allows for 21% of that uptake to be new uptake, all other uptake must be from substitutes to avoid having more than 100% uptake. Another example is the vitamin D uptake in pregnant women (before and after 10 weeks); this baseline uptake is 42.3%, so an increase of 50% Healthy Start uptake (with a substitution coefficient of 0%) still has capacity to benefit. However, when the uptake reaches 60%, some of these supplement takers must be substitutes to avoid the uptake increasing over 100%.

The table also shows that, the lower the substitution coefficient (i.e. the more new uptakers there are), the more cost-effective the intervention. This applies up to 90% Healthy Start uptake, at which point the ICER stays the same because there is no more capacity to benefit. A decrease in the substitution coefficient cannot have a negative effect on the cost-effectiveness, it can only decrease the ICER, or the ICER stays the same.

The ERG requested that an estimate of how much the uptake needs to increase by and how many of these need to be new users was made. Table 5.16 above demonstrates that the uptake and the number that are new users have a large impact on the cost-effectiveness. It is also important to note that this two-way sensitivity analysis is dependent on many other uncertain parameters in the model.

**Table 5.17: Healthy Start uptake and substitution coefficient – Infants and children**

| | | Change in HS uptake - children | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
| Substitute coefficient | 0% | £556 | £3,454 | £8,040 | £13,703 | £20,056 | £26,849 | £33,923 | £41,177 | £48,546 | £55,990 | £63,545 |
| | 10% | £556 | £3,517 | £8,120 | £13,780 | £20,122 | £26,902 | £33,964 | £41,208 | £48,568 | £56,005 | £63,545 |
| | 20% | £556 | £3,580 | £8,201 | £13,859 | £20,190 | £26,957 | £34,006 | £41,240 | £48,592 | £56,022 | £63,545 |
| | 30% | £556 | £3,643 | £8,284 | £13,940 | £20,260 | £27,014 | £34,051 | £41,274 | £48,617 | £56,040 | £63,545 |
| | 40% | £556 | £3,707 | £8,368 | £14,022 | £20,332 | £27,073 | £34,098 | £41,309 | £48,644 | £56,060 | £63,545 |
| | 50% | £556 | £3,771 | £8,453 | £14,107 | £20,407 | £27,135 | £34,147 | £41,347 | £48,673 | £56,081 | £63,545 |
| | 60% | £556 | £4,358 | £8,807 | £14,312 | £20,523 | £27,199 | £34,181 | £41,364 | £48,680 | £56,084 | £63,545 |
| | 70% | £556 | £4,986 | £9,184 | £14,528 | £20,645 | £27,265 | £34,216 | £41,381 | £48,688 | £56,086 | £63,545 |
| | 80% | £556 | £5,657 | £9,584 | £14,757 | £20,772 | £27,335 | £34,252 | £41,399 | £48,695 | £56,089 | £63,545 |
| | 90% | £556 | £6,375 | £10,010 | £14,998 | £20,906 | £27,407 | £34,289 | £41,417 | £48,703 | £56,091 | £63,545 |
| | 100% | £556 | £7,142 | £10,464 | £15,252 | £21,046 | £27,481 | £34,327 | £41,435 | £48,711 | £56,094 | £63,545 |

Table 5.17 shows the effect of varying the change in Healthy Start uptake and the substitution coefficient in the subgroups with infants and children. Similarly to Table 5.16, a decrease in the substitution coefficient (that is an increase in the number of new uptakers) either decreases the ICER, or it remains the same. Table 5.17 shows that, as the Healthy Start uptake in children increases, moving the Healthy Start scheme to universal provision is less likely to be cost-effective. The reason for this is that the subgroups with infants and children do not receive any QALY gain from supplementation in the model, as folic acid is the only vitamin to which a QOL benefit could be assigned. So in the model, the higher the uptake is for children, the higher the costs of supplementation are, without any benefits to QOL.

## 5.5 THREE-WAY SENSITIVITY ANALYSIS

**Key messages from Three-Way Sensitivity Analysis (Scenario 2):**

- Three-way analyses were undertaken around the three key drivers of the analysis – substitution coefficient, QALY loss associated with vitamin D and proportion of pregnancies affected by a NTD resulting in termination;
- The model results are highly sensitive to these three parameters. Threshold values for cost-effectiveness are provided in Table 5.18.

There are many uncertainties in the economic model and this has been addressed with sensitivity and scenario analyses. Due to the number of sensitivity analyses that it is necessary to carry out, three of the most important drivers of the model have been selected and presented in a three-way sensitivity analysis. This three-way sensitivity analysis provides a diagram summarising the effect of three key drivers in the model. The sensitivity analysis was run with all current and extended subgroups included and all the base case values described earlier in the report from the public sector perspective.

The three parameters that have been varied in the three-way sensitivity analysis are:

- The substitution coefficient (whether Healthy Start vitamin supplement takers are newly taking vitamins, or were taking privately purchased vitamins previously);
- The QALY loss associated with vitamin D;
- The proportion of pregnancies affected by a NTD that result in a termination.

The substitution coefficient is varied between 0% and 100% in each graph (base case value: 0%). This is shown by the blue line on each graph. The QALY loss for vitamin D is varied between no QALY loss and 0.2 QALY loss for symptomatic vitamin D deficiency (base case value: QALY loss not included). Threshold analysis of the QALY loss for symptomatic vitamin D is in Section 5.3.4. The QALY loss can be read along the graphs from left to right. The proportion of pregnancies affected by a NTD that result in a termination was varied from 80% to 100% (base case value 80%. When the number of terminations increases, an adjustment is automatically made to reduce the number of spina bifida births. The proportion of pregnancies affected by a NTD that result in termination can be read from top to bottom in Diagram 5.1.

## Diagram 5.1: Three-way sensitivity analysis

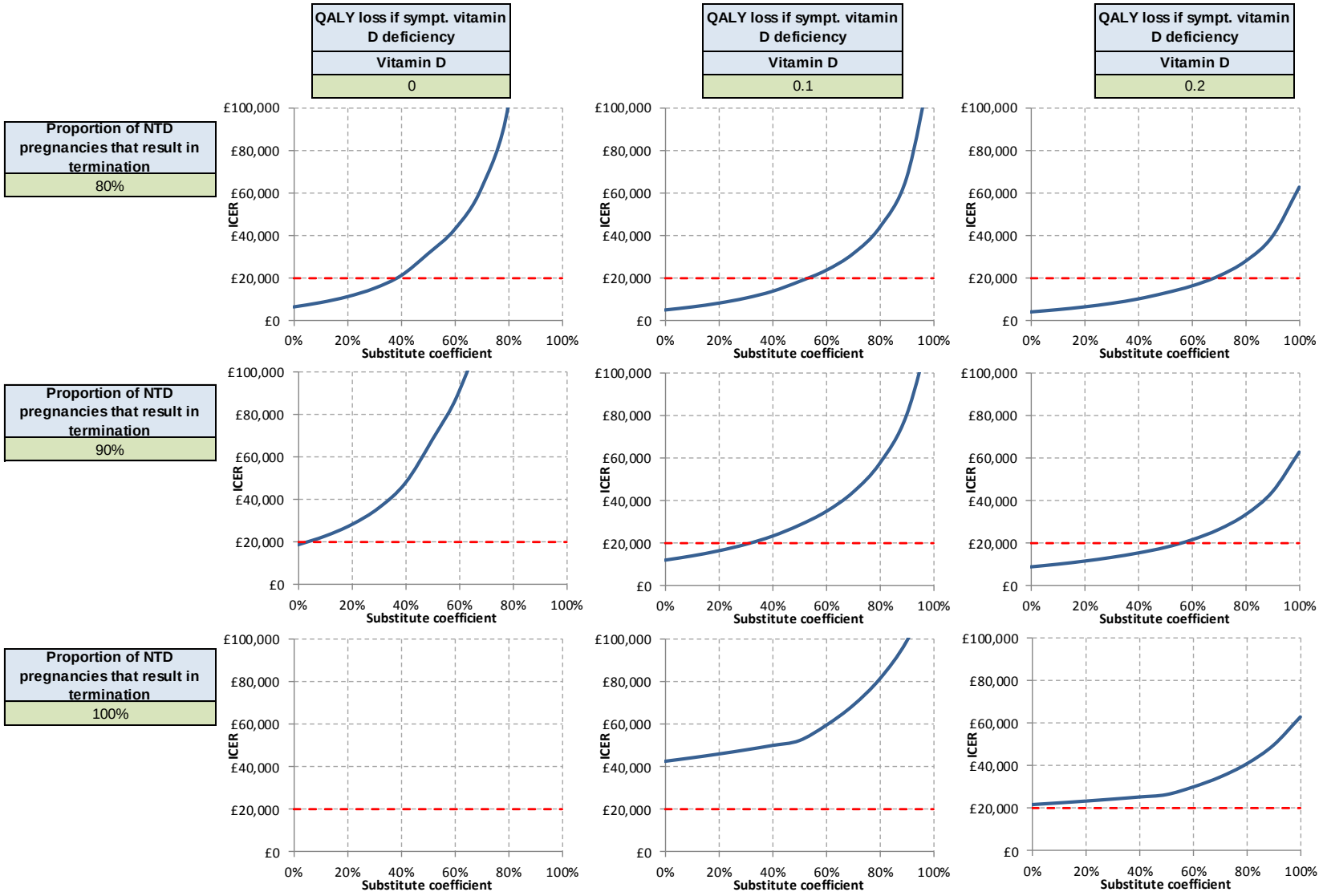


Diagram 5.1 illustrates the effects that varying the three parameters has on the ICER. Table 5.18 shows the (approximate) highest substitution coefficient for which the intervention is likely to be cost-effective in each scenario. The diagram shows that the greater the QALY loss is for symptomatic vitamin D deficiency, the lower the ICER is. It also shows that the higher the proportion of pregnancies affected by a NTD that result in termination, the higher the ICER will be. In the bottom left-hand graph, even when the substitution coefficient is 0% (that is, all incremental Healthy Start uptake comes from new uptakers), moving to a universal scheme is unlikely to be cost-effective. This graph does not display a line because the y-axis is set at £100,000. In this scenario, the ICER is always above £100,000. In the top right-hand graph, moving to a universal scheme is likely to be cost-effective even if the substitute coefficient is as high as around 95%. This diagram shows that the effect of varying the proportion of terminations and the substitution coefficient has less of an influence in the scenario where QALY loss is assigned to symptomatic vitamin D deficiency. This is because when the QALYs for vitamins other than folic acid are included, the number of terminations (which is affected by the folic acid intake) and the substitution coefficient have less weight in the model. A paucity of data means QALY losses were not assigned to vitamin D deficiency, except in an exploratory analysis in Section 5.3.4.

**Table 5.18: Highest substitution coefficient to remain cost-effective**

| | **QALY loss if below LRNI or if vitamin D deficient** | | |
|---|---|---|---|
| **Proportion of pregnancies affected by a NTD that result in termination** | **Vitamin D** 0 | **Vitamin D** 0.1 | **Vitamin D** 0.2 |
| 80% | 40% | 55% | 70% |
| 90% | 10% | 30% | 60% |
| 100% | NA | NA | NA |

# Section 6: Discussion

The results of the model estimate that if the Healthy Start scheme were to be implemented universally compared to current provision it would be cost-effective if it was extended to any combination of current or additional subgroups as long as that combination includes 'women planning a pregnancy and before 10 weeks pregnant'. Therefore, it is estimated that it is not cost-effective in scenario 1 and it would be cost-effective in scenario 2 where 'women planning a pregnancy and before 10 weeks pregnant' are included. There is a lot of uncertainty in the economic model. Many of the model inputs are uncertain due to a lack of data and a lack of information on how a universal scheme would be implemented. Therefore, arbitrary data have been used for some inputs as described previously. These results are particularly limited in that the distribution route of the scheme for women planning a pregnancy and those less than 10 weeks pregnant is unknown. It has been assumed within the model that Healthy Start vitamin supplements are delivered to these women in the same way as the current scheme with no additional costs incurred. Should reaching these women incur costs above and beyond those of the current subgroups, the universal scheme will be less cost-effective.

The results of the model estimate that it is not cost-effective to extend the scheme universally within the current subgroups (all pregnant women from 10 weeks; women with a child under 12 months; and children over 6 months and under 4 years) (scenario 1). These results are driven by the lack of QALY loss averted by the scheme. Providing folic acid to women who are at least 10 weeks pregnant is too late to reduce pregnancies affected by a NTD successfully. It is important to note that the model only assigns a QALY change due to supplementation of women via the proportion of pregnancies affected by a NTD. This is also dependent on their termination rate. QALYs are not assigned to any health benefits from supplementation with vitamins A, C or D. This does not mean that there are no QOL benefits, only that the data are not available to describe the health benefits in a quantitative fashion.

Three key drivers of the model results have been identified. Firstly, the number of pregnancies affected by a NTD that result in termination. When the number of terminations decreases, the number of spina bifida births increases, making the cost per pregnancy affected by a NTD higher. Therefore, the higher the proportion of terminations, the less cost-effective the scheme becomes. Secondly, a key driver is whether a QALY loss can be assumed and assigned to those with symptomatic vitamin D deficiency. The higher the QALY loss assumed per person, the more cost-effective the scheme becomes. Thirdly, the substitution coefficient. This accounts for the number of people that take Healthy Start vitamin supplements in place of vitamins they previously purchased privately. The higher the substitution coefficient, the less likely the scheme is to be cost-effective because more people are substituting (extra cost to the public sector for no extra benefit). Finally, these three uncertainties (and all the other uncertainties in the model) interact. It is not possible to show every permutation of the results. However, the sensitivity analyses do show that if it is

reasonable to assume there is an impact on QALYs for vitamin D, the effect of varying the substitution coefficient and the proportion of pregnancies affected by a NTD that result in a termination becomes much less pronounced. A threshold analysis was carried out to examine the effect of adding QALY loss to symptomatic vitamin D deficiency alone (without any QALY loss assigned to vitamins A and C). In scenario 1, with the base case inputs, this analysis estimated that the QALY loss would need to be over approximately 0.27 per case of symptomatic vitamin D deficiency to make the scheme cost-effective at a £20,000 threshold.

The model report includes many sensitivity and scenario analyses to account for the uncertainty in the model, the most important of which have been discussed above. Based on the model results it is not possible to say with certainty if moving the Healthy Start scheme from a targeted scheme to universal provision would be cost-effective. However, the model results suggest that moving to a universal scheme could be cost-effective for some subgroup combinations, specifically, for women planning a pregnancy and less than 10 weeks pregnant.

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# APPENDIX A

## Primary Data Collection – Example survey Questions

# Example survey Questions

Note that where question filtering applies, (such as, if the participant answers X to question X), the participants will not see this text, they will automatically be directed to the correct question based on their answer.

Screening question: Are you planning a pregnancy?

**Questions for women planning a pregnancy**

1. Are you eligible for **free** Healthy Start vitamin supplements?
   a) Yes - because I qualify for the Healthy Start scheme
   b) Yes – because free Healthy Start vitamins are made available to all women planning a pregnancy in the area where I live
   c) Yes – but I am not sure why I qualify for free Healthy Start vitamins
   d) No
   e) I don't know

If yes (a, b or c), continue to question 2. Otherwise, go to question 3.

2. Do you take up on the offer of **free** Healthy Start vitamin supplements?
   - Always
   - Most of the time
   - Occasionally
   - Never

3. Do you qualify for any other type of free vitamin scheme (other than Healthy Start)?
   Yes (Please give details of the scheme – text box)
   No

   If yes, go to next question. If no, go to question 5.

4. Do you take up on this offer?
   - Always
   - Most of the time
   - Occasionally
   - Never

5. Do you ever **buy** vitamin supplements for yourself?
   - Always
   - Most of the time
   - Occasionally
   - Never

If never, go to question 15. Otherwise continue to question 6.

6. Please tick which (if any) of the following benefits you are in receipt of.
   a) Income-based jobseeker's allowance
   b) Income-related employment and support allowance
   c) Income support
   d) Working tax credits
   e) Working tax credit run-on
   f) Child tax credit **and** you have an annual family income of over £16,190
   g) Child tax credit **and** you have an annual family income of £16,190 or less
   h) Housing benefit
   i) Universal credit

7. Did you take vitamin supplements *before* you were planning a pregnancy?
   Yes / No

8. Do you take vitamin supplements now that you are planning a pregnancy?
   Yes / No / I don't know

If yes, continue with survey, if no question 15.

9. If yes to Q8: Which of the following best describes the vitamin supplement you are currently taking:
   - A single supplement, for example tablets containing folic acid only
   - A multivitamin supplement
   - I don't know

10. If yes to Q8, do the vitamin supplements that you are currently taking contain:

    a) Folic acid? Yes/ No/ I don't know
    b) Vitamin C? Yes/No /I don't know
    c) Vitamin D? Yes/No/I don't know

11. If yes to Q8, which of the following best describes how frequently you take the vitamin supplements?
    a) I always take them as recommended on the pack
    b) Most of the time, I take them as recommended on the pack
    c) I occasionally take them as recommended on the pack
    d) I don't take them.

12. If yes to Q8: If you know the brand name of the vitamin supplement(s) you are taking, please write it in the text box below.

13. If yes to Q8: Where do you get your vitamin supplement from?
    - I buy it;
    - Someone buys it for me;

- I receive a free prescription for it;
- I pay for it on prescription.

14. If respondents select private purchase (i.e. they choose option 1, 2 or 4 to question 13) they will answer the following question: Please state approximately how much you pay per pack for your supplements and approximately how many tablets are in a pack. If you do not know the price or number of tablets, please leave this question blank.
    Text box to enter price
    Text box to enter number of tablets.

15. Is there anything else you would like to tell us about your current vitamin supplementation?

**Questions for pregnant women**

1. Are you eligible for **free** Healthy Start vitamin supplements?
   f) Yes - because I qualify for the Healthy Start scheme
   g) Yes – because free Healthy Start vitamins are made available to all pregnant women in the area where I live
   h) Yes – but I am not sure why I qualify for free Healthy Start vitamins
   i) No
   j) I don't know

If yes, continue to question 2. Otherwise, go to question 3.

2. Do you take up on the offer of **free** Healthy Start vitamin supplements?
   - Always
   - Most of the time
   - Occasionally
   - Never

3. Do you qualify for any other type of free vitamin scheme (other than Healthy Start)?
   Yes (Please give details of the scheme – text box)
   No

   If yes, go to next question. If no, go to question 5.

4. Do you take up on this offer?
   - Always
   - Most of the time
   - Occasionally
   - Never

5. Do you ever **buy** vitamin supplements for yourself?
   - Always
   - Most of the time
   - Occasionally
   - Never

If never, go to question 16. Otherwise continue to question 6.

6. Please tick which (if any) of the following benefits you are in receipt of.
   **j)** Income-based jobseeker's allowance
   **k)** Income-related employment and support allowance
   **l)** Income support
   **m)** Working tax credits
   **n)** Working tax credit run-on
   **o)** Child tax credit **and** you have an annual family income of over £16,190
   **p)** Child tax credit **and** you have an annual family income of £16,190 or less
   **q)** Housing benefit

**r)** Universal credit

7. Did you take vitamin supplements *before* you were planning a pregnancy?
Yes / No

8. Did you take vitamin supplements *when* you were planning a pregnancy?
Yes / No

9. Do you take any vitamin supplements now that you are pregnant?
Yes / No

If yes, continue with survey, if no question 16.

10. If yes to Q9: Do the vitamin supplements that you are currently taking contain:
    a) Folic acid? Yes / No / I don't know
    b) Vitamin C? Yes / No / I don't know
    c) Vitamin D? Yes / No / I don't know

11. If yes to Q9: which of the following best describes how frequently you take the vitamin supplements?
    a. I always take them as recommended on the pack
    b. Most of the time, I take them as recommended on the pack
    c. I occasionally take them as recommended on the pack
    d. I don't take them.

12. If yes to Q9: Which of the following best describes the vitamins you are currently taking:
    - Single supplements (for example a tablet containing folic acid or vitamin D only );
    - A multivitamin supplement
    - I don't know

13. If yes to Q9: If you know the brand name of the vitamin supplement(s) you are taking, please write it in the text box below.

14. If yes to Q9: Where do you get your vitamin supplement from?
    - I buy it;
    - Someone buys it for me;
    - I receive a free prescription for it;
    - I pay for it on prescription.

15. If respondents select private purchase ( i.e. they choose option 1, 2 or 4 to question 14) they will answer the following question: Please state approximately how much you pay per pack for your supplements and approximately how many tablets are in

a pack. If you do not know the price or number of tablets, please leave this question blank.
Text box to enter price
Text box to enter number of tablets.

16. Is there anything else you would like to tell us about your current vitamin supplementation?

**Questions for women with children aged 0-5**

1. Screening question: Do you have any children aged under five years in your household?
   Yes / No

   If no, survey ends. If yes, continue to question 2.

2. Are you or the children in your household eligible for **free** Healthy Start vitamin supplements? (please tick all that apply)
   a) Yes - because I/we qualify for the Healthy Start scheme
   b) Yes – because Healthy Start vitamins are made available for free in the area where I live
   c) Yes – but I am not sure why I/we qualify for free Healthy Start vitamins
   d) No
   e) I don't know

2a. (If yes) Please select who qualifies for free Healthy Start supplements (tick all that apply)
   You
   Your children

If yes, continue to question 3. Otherwise, go to question 4.

3. Do you take up on the offer of **free** Healthy Start vitamin supplements?
   - Always
   - Most of the time
   - Occasionally
   - Never

4. Do you/your child qualify for any other type of free vitamin scheme (other than Healthy Start)?
   Yes (Please give details of the scheme including who qualifies – text box)
   No

   If yes, go to next question. If no, go to question 6.

5. Do you take up on this offer?
   - Always
   - Most of the time
   - Occasionally
   - Never

6. Do you ever **buy** vitamin supplements for:
   Yourself - Always / most of the time / occasionally / never
   Your children - Always / most of the time / occasionally / never

If never on both, go to question 25. Otherwise continue to question 7. If never on 'yourself' is selected, skip 'Women's supplementation' section. If never on 'your child' is selected skip 'Children's supplementation'.

7. Please tick which (if any) of the following benefits you are in receipt of.
   a) Income-based jobseeker's allowance
   b) Income-related employment and support allowance
   c) Income support
   d) Working tax credits
   e) Working tax credit run-on
   f) Child tax credit **and** you have an annual family income of over £16,190
   g) Child tax credit **and** you have an annual family income of £16,190 or less
   h) Housing benefit
   i) Universal credit

8. Is your youngest child under 12 months old?
   Yes/No

   If no, go to question 16 (children), if yes continue to question 9.

<u>Women's supplementation</u>

9. Do you currently take any vitamin supplements?
   Yes / No

   If yes, carry onto question 10, if no go to question 16.

10. If yes to Q9: Do the vitamin supplements that you are currently taking contain:
    a) folic acid? Yes / No / I don't know
    b) vitamin C? Yes / No / I don't know
    c) vitamin D? Yes / No / I don't know

11. If yes to Q9: which of the following best describes how frequently you take the vitamin supplements?
    a. I always take them as recommended on the pack
    b. Most of the time, I take them as recommended on the pack
    c. I occasionally take them as recommended on the pack
    d. I don't take them.

12. If yes to Q9: Which of the following best describes the vitamins you are currently taking:
    - Single supplements (for example a tablet containing vitamin D only);
    - A multivitamin supplement
    - I don't know

13. If yes to Q9: If you know the brand name of the vitamin supplement you are taking, please write it in the text box below.

14. If yes to Q9: Where do you get your vitamin supplement from?
    - I buy it;
    - Someone buys it for me;
    - I receive a free prescription for it;
    - I pay for it on prescription.

15. If respondents select private purchase (i.e. they choose option 1, 2 or 4 to question 13) they will answer the following question: Please state approximately how much you pay per pack for your supplements and approximately how many tablets are in a pack. If you do not know the price or number of tablets, please leave this question blank.
    Text box to enter price
    Text box to enter number of tablets.

Children's supplementation

16. Do your children currently take any vitamin supplements?
    Yes / No

If no go to question 25, if yes continue to question 17.

17. What are the ages of any infants or children you have who are under 5 years old who are currently taking vitamin supplements?
    Child 1

    - 0 to 6 months;
    - Over 6 months to 12 months
    - Over 1 year to under 4 years
    - Over 4 years and under 5 years.

    Child 2 – Age etc.

When answering questions 18 to 24 if respondents have indicated they give vitamin supplementation to more than one child they will be asked to think about each of their children in turn.

18. If option 1 or 2 was selected for question 17. Please tick all the options that currently apply to your baby:
    My baby is breastfed
    My baby receives formula
    My baby is given vitamin supplements

19. Do the vitamin supplements that you are currently giving to your child contain:
    a) vitamin A? Yes / No / I don't know
    b) vitamin C? Yes / No / I don't know
    c) vitamin D? Yes / No / I don't know

20. Which of the following best describes how frequently your child takes the vitamin supplements?
    a. They always take them as recommended on the pack
    b. Most of the time, they take them as recommended on the pack
    c. They occasionally take them as recommended on the pack
    d. They don't take them.

21. Which of the following best describes the vitamins you are currently giving to your child:
    - Single supplements (for example drops or a tablet containing vitamin D only);
    - A multivitamin supplement
    - I don't know

22. If you know the brand name of the vitamin supplement your child is taking, please write it in the text box below.

23. Where do you get your child's vitamin supplement from?
    - I buy it
    - Someone buys it for me
    - I receive a free prescription for it

24. If private purchase (option 1 or 2) to question 23: Please state approximately how much you pay per pack for your child's supplements and approximately how many tablets or doses are in a pack. If you do not know the price or number of tablets, please leave this question blank.
    Text box to enter price
    Text box to enter number of tablets.

25. Is there anything else you would like to tell us about your or your child/children's current vitamin supplementation?

# APPENDIX B

# Coefficient Technical Appendix

# Technical Appendix – Substitution coefficient

## Background

Even without Healthy Start provision, some people already take vitamin supplements. In some cases, a relatively high proportion of people take vitamin supplements (e.g. folic acid when pregnant), as evidenced by the baseline uptake of vitamin supplements. Due to this, when the increase in uptake of *Healthy Start* vitamin supplements is modelled, it is important to take into account where this *extra* uptake comes from. The uptake of Healthy Start vitamin supplements might come from people who previously did not take vitamin supplements at all, or it might come from people who are already taking vitamin supplements (i.e. they were purchasing them privately or receiving them on prescription).

When the extra Healthy Start uptake comes from those who *already* take vitamins this means that there is an extra cost to the public sector of providing the Healthy Start vitamin supplements but no actual health benefit (the person taking the vitamin supplement is simply substituting privately purchased vitamin supplements for the free Healthy Start vitamin supplements). The substitution coefficient described below allows for this scenario to be modelled.

The following examples and graphs show how the coefficient is applied. The numbers in the graphs are illustrative for easier interpretation and do not represent the baseline uptake in the economic model.

## Substitution coefficient

To allow a number of different scenarios to be modelled, a substitution 'coefficient' is used in the model. The coefficient can be varied between 0% and 100%, with each value offering a specific assumption about the source of Healthy Start uptake. Please note that the coefficient value does **not** represent the *actual* level of uptake. In short, the interpretation of each coefficient value is as follows:

Substitution = 0%: Uptake of Healthy Start is from new uptakers wherever possible;
Substitution = 50%: Uptake of Healthy Start is derived proportionally[9] from substitutes and new uptakers;
Substitution = 100%: Uptake of Healthy Start comes from substitutes wherever possible.

For instance, suppose the current level of uptake is 70% and the Healthy Start uptake is 20%. If a substitution coefficient of 100% is selected, then the 'new' uptake will be 70% (this suggests that all of the new Healthy Start users were drawn from people who already paid privately). If a substitution coefficient of 0% is selected, then the 'new' uptake will be 90%. If a substitution coefficient of 50% is selected, then the 'new' uptake will be 76% (this is because the 20% was split *proportionally*, i.e. 70%-30% between substituters and new uptakers).

The substitution coefficient approach was used since the baseline level of uptake is likely to be very different for each vitamin. The following examples illustrate how the different coefficients would work in practice.

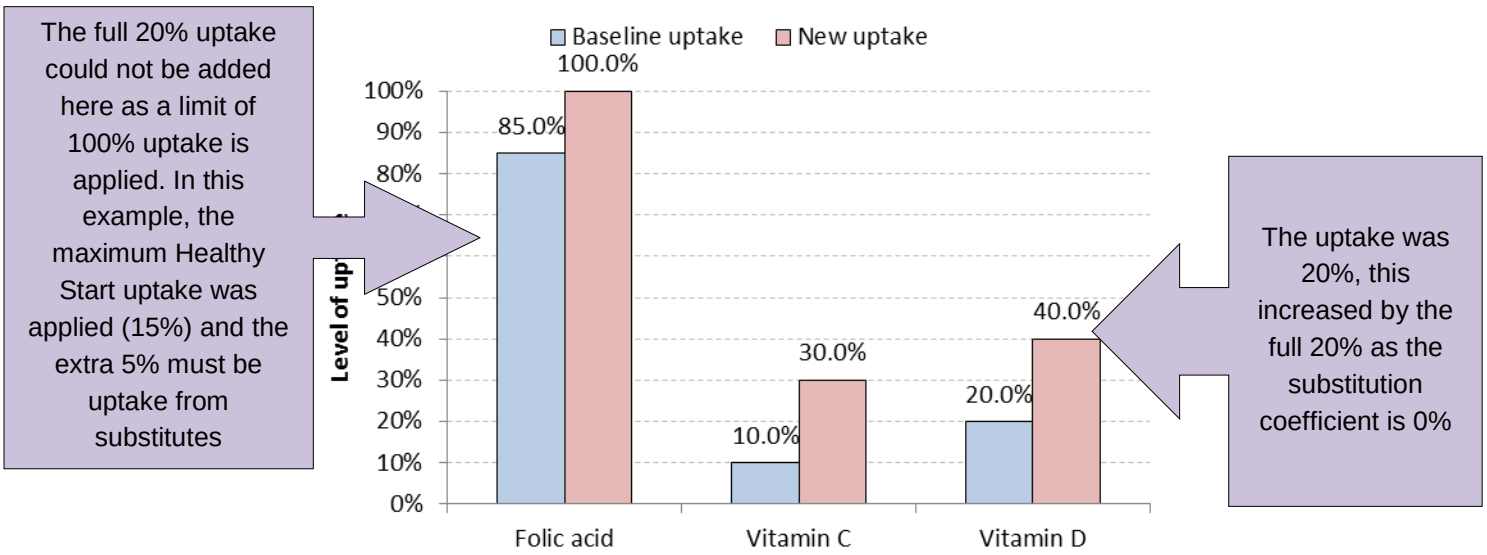
[9] Meaning that the new Healthy Start users will be assumed to come proportionally from those already taking vitamins and new uptakers. If, for instance, the current uptake was high, then the Healthy Start uptakers would be more likely to come from those already taking supplements.

**Substitution coefficient of 0%**

When the substitution coefficient is 0% this means that 100% of the increase in Healthy Start uptake is from new uptakers. Graph A.1 below shows the change in the uptake of all vitamin supplements from the current targeted offering to the universal offering with:

- An increase in Healthy Start uptake of **20%;**
- A substitution coefficient of **0%.**

**Graph A.1: Substitution coefficient of 0%**

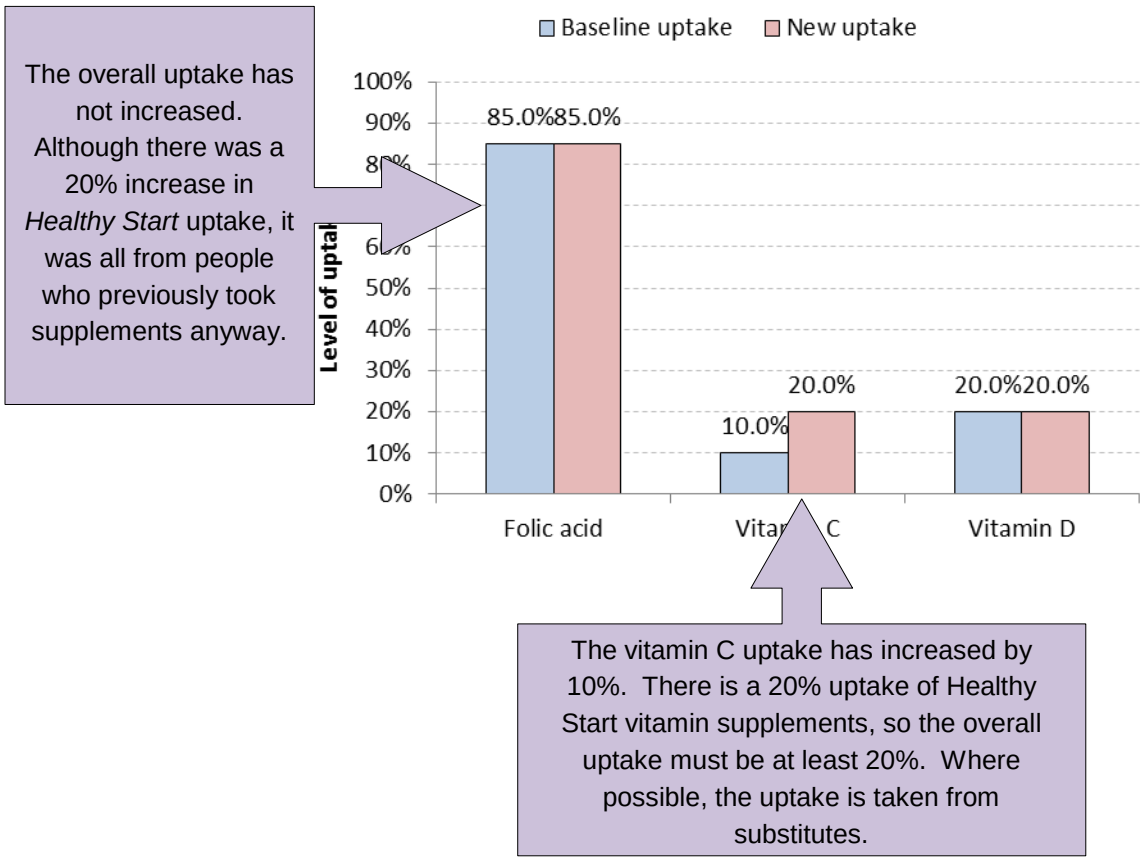



**Substitution coefficient of 100%**

When the substitution coefficient is 100%, this means that all extra Healthy Start uptake is from substitutes. Graph A.2 shows how the overall vitamin supplement uptake changes when there is:

- An increase in Healthy Start uptake of **20%;**
- A substitution coefficient of **100%.**

**Graph A.2: Substitution coefficient of 100%**

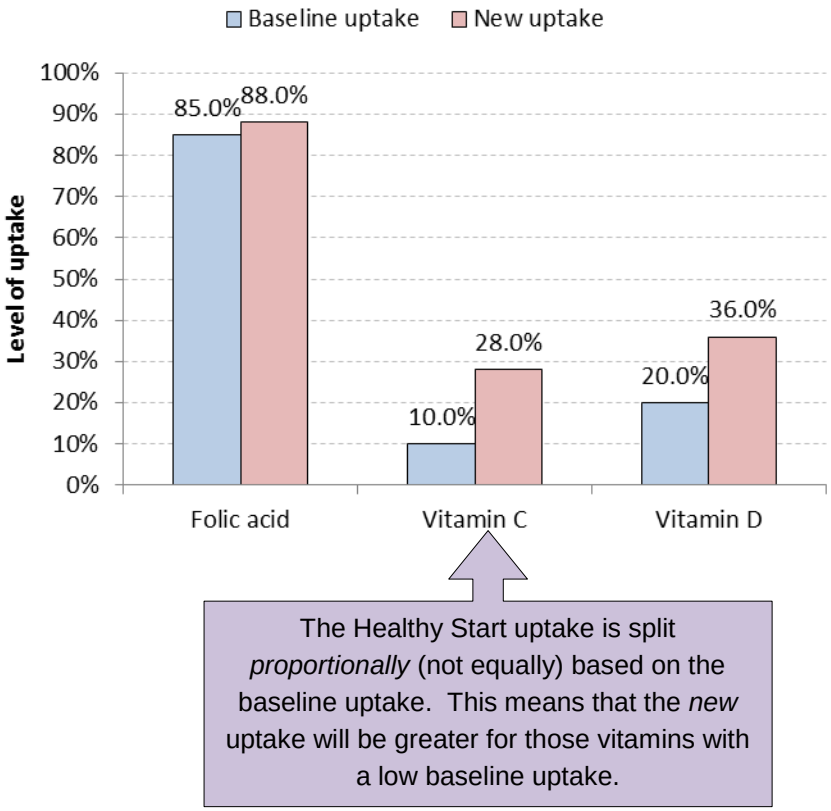



**Substitution coefficient of 50%**

When the substitution coefficient is 50%, the model assumes that Healthy Start uptake is split *proportionally* between new uptake and substitutes. Graph A.3 shows the baseline uptake and new level of uptake when there is:

- An increase in Healthy Start uptake of **20%;**
- A substitution coefficient of **50%.**

**Graph A.3: Substitution coefficient of 50%**




**All other substitution coefficients**

All other numbers interpolate between the assumptions outlined above. For example:

- A substitution coefficient of 25% is hallway between a substitution coefficient of 0% and 50%;
- A substitution coefficient of 75% is halfway between a substitution coefficient of 50% and 100%.

# APPENDIX C

## Detailed Results Breakdown

# Results Breakdown

**Detailed results from Section 5.1.3**

**Offering Healthy Start supplements universally to current subgroups +women planning (and before 10 weeks pregnant)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £5,694,496 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £5,464,530 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £52,078,680 | £42,456,430 | -£9,622,250 |
| **Total incremental cost** | | | **£4,211,201** |
| QALYs lost (pregnancy affected by a NTD) | 6,870 | 6,120 | -750 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **750** |
| **ICER** | | | **£5,618** |
| Number of people below vitamin A LRNI | 113,316 | 92,430 | -20,886 |
| Number of people below vitamin C LRNI | 40,458 | 29,783 | -10,675 |

* The incremental cost only was calculated.

**Offering Healthy Start supplements universally to current subgroups + pregnant women before 10 weeks**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £5,209,214 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £5,069,184 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £48,486,240 | £42,372,695 | -£6,113,544 |
| **Total incremental cost** | | | **£6,839,279** |
| QALYs lost (pregnancy affected by a NTD) | 6,386 | 6,143 | -243 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **243** |
| **ICER** | | | £28,185 |
| Number of people below vitamin A LRNI | 113,316 | 92,430 | -20,886 |
| Number of people below vitamin C LRNI | 35,912 | 26,423 | -9,489 |

* The incremental cost only was calculated.

**Offering Healthy Start supplements universally to current subgroups + infants aged 0 to 6 months**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £5,295,784 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £4,826,015 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £31,774,712 | £26,847,056 | -£4,927,656 |
| **Total incremental cost** | | | **£7,868,568** |
| QALYs lost (pregnancy affected by a NTD) | 3,635 | 3,623 | -13 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **13** |
| **ICER** | | | £620,392 |
| Number of people below vitamin A LRNI | 113,706 | 92,748 | -20,958 |
| Number of people below vitamin C LRNI | 29,123 | 21,860 | -7,263 |

* The incremental cost only was calculated.

**Offering Healthy Start supplements universally to current subgroups + children aged 4 to 5 years**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £6,096,732 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £5,121,437 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £32,526,833 | £27,198,334 | -£5,328,499 |
| **Total incremental cost** | | | **£8,564,095** |
| QALYs lost (pregnancy affected by a NTD) | 3,635 | 3,623 | -13 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **13** |
| **ICER** | | | £675,230 |
| Number of people below vitamin A LRNI | 144,802 | 117,833 | -26,968 |
| Number of people below vitamin C LRNI | 29,123 | 21,860 | -7,263 |

* The incremental cost only was calculated.

**Offering Healthy Start supplements universally to current subgroups + all extended subgroups (Scenario 2)**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £7,136,203 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £6,148,818 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £54,786,787 | £43,721,249 | -£11,065,538 |
| **Total incremental cost** | | | **£4,893,907** |
| QALYs lost (pregnancy affected by a NTD) | 6,870 | 6,120 | -750 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **750** |
| **ICER** | | | **£6,528** |
| Number of people below vitamin A LRNI | 145,193 | 118,152 | -27,041 |
| Number of people below vitamin C LRNI | 40,458 | 29,783 | -10,675 |

* The incremental cost only was calculated.

**Detailed results from Section 5.1.2**

**Offering Healthy Start supplements universally to women planning (and before 10 weeks pregnant) only**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £719,091 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £832,948 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £21,281,961 | £16,066,144 | -£5,215,817 |
| **Total incremental cost** | | | **-£989,352** |
| QALYs lost (pregnancy affected by a NTD) | 3,234 | 2,497 | -737 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **737** |
| **ICER** | | | **Dominant** |
| Number of people below vitamin A LRNI | 0 | 0 | 0 |
| Number of people below vitamin C LRNI | 11,335 | 7,924 | -3,411 |

* The incremental cost only was calculated.

**Offering Healthy Start supplements universally to pregnant women before 10 weeks only**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £233,809 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £437,602 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £17,689,521 | £15,982,410 | -£1,707,111 |
| **Total incremental cost** | | | **£1,638,111** |
| QALYs lost (pregnancy affected by a NTD) | 2,750 | 2,520 | -230 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **230** |
| **ICER** | | | **£7,126** |
| Number of people below vitamin A LRNI | 0 | 0 | 0 |
| Number of people below vitamin C LRNI | 6,789 | 4,563 | -2,226 |

* The incremental cost only was calculated.

**Offering Healthy Start supplements universally to infants aged 0 to 6 months only**

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £320,379 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £194,433 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £977,993 | £456,771 | -£521,222 |
| **Total incremental cost** | | | **£2,668,015** |
| QALYs lost (pregnancy affected by a NTD) | 0 | 0 | 0 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **0** |
| **ICER** | | | **Infinite** |
| Number of people below vitamin A LRNI | 391 | 319 | -72 |
| Number of people below vitamin C LRNI | 0 | 0 | 0 |

* The incremental cost only was calculated.

### Offering Healthy Start supplements universally to children aged 4 to 5 years only

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £1,121,327 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £489,855 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £1,730,114 | £808,048 | -£922,066 |
| **Total incremental cost** | | | **£3,363,541** |
| QALYs lost (pregnancy affected by a NTD) | 0 | 0 | 0 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **0** |
| **ICER** | | | **Infinite** |
| Number of people below vitamin A LRNI | 31,486 | 25,404 | -6,083 |
| Number of people below vitamin C LRNI | 0 | 0 | 0 |

* The incremental cost only was calculated.

### Offering Healthy Start supplements universally to all extended subgroups only

| Summary table | Targeted | Universal | Incremental |
|---|---|---|---|
| Cost of HS vitamins | NA* | NA* | £2,160,798 |
| Private purchase cost of vitamins | £0 | £0 | £0 |
| Cost of intervention (distribution) | NA* | NA* | £1,517,236 |
| Cost of intervention (set up) | £0 | £2,674,425 | £2,674,425 |
| Cost of treatment (NTDs, vitamin D deficiency) | £23,990,068 | £17,330,963 | -£6,659,105 |
| **Total incremental cost** | | | **-£306,646** |
| QALYs lost (pregnancy affected by a NTD) | 3,234 | 2,497 | -737 |
| Vitamin A | 0 | 0 | 0 |
| Vitamin C | 0 | 0 | 0 |
| Vitamin D deficiency | 0 | 0 | 0 |
| **Total QALYs gained** | | | **737** |
| **ICER** | | | **Dominant** |
| Number of people below vitamin A LRNI | 31,877 | 25,722 | -6,155 |
| Number of people below vitamin C LRNI | 11,335 | 7,924 | -3,411 |

* The incremental cost only was calculated.

# APPENDIX D

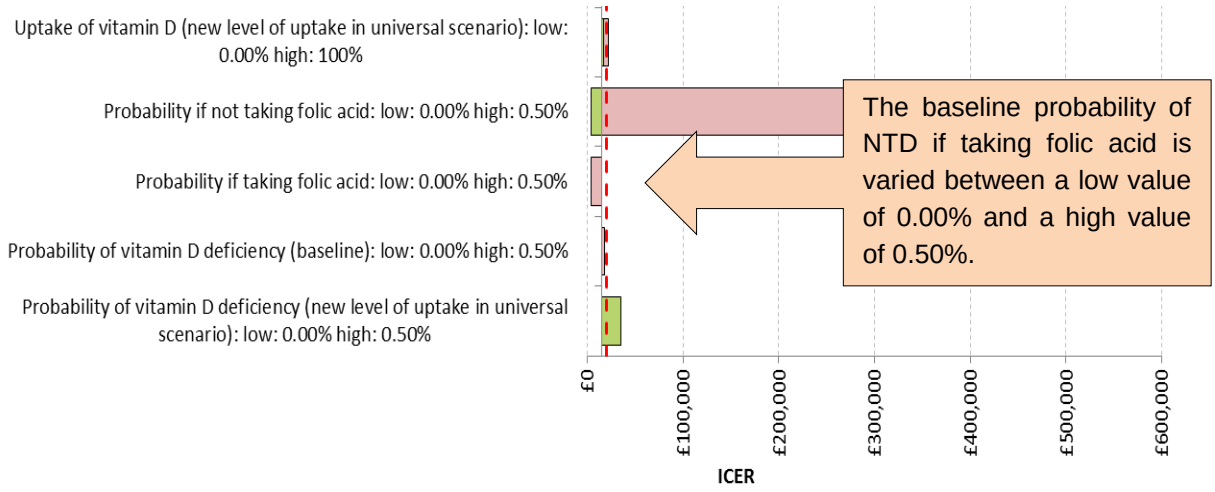
# Tornado Diagrams User Guide

# Tornado Diagrams

Tornado diagrams are a useful tool for presenting the results of univariate sensitivity analyses around multiple model input parameters on one graph. This can allow the reviewer to assess which of the model input parameters have the greatest influence on the model's results. A step-by-step guide to interpreting a tornado diagram is now presented using the pregnant women after 10 weeks subgroup as an example.

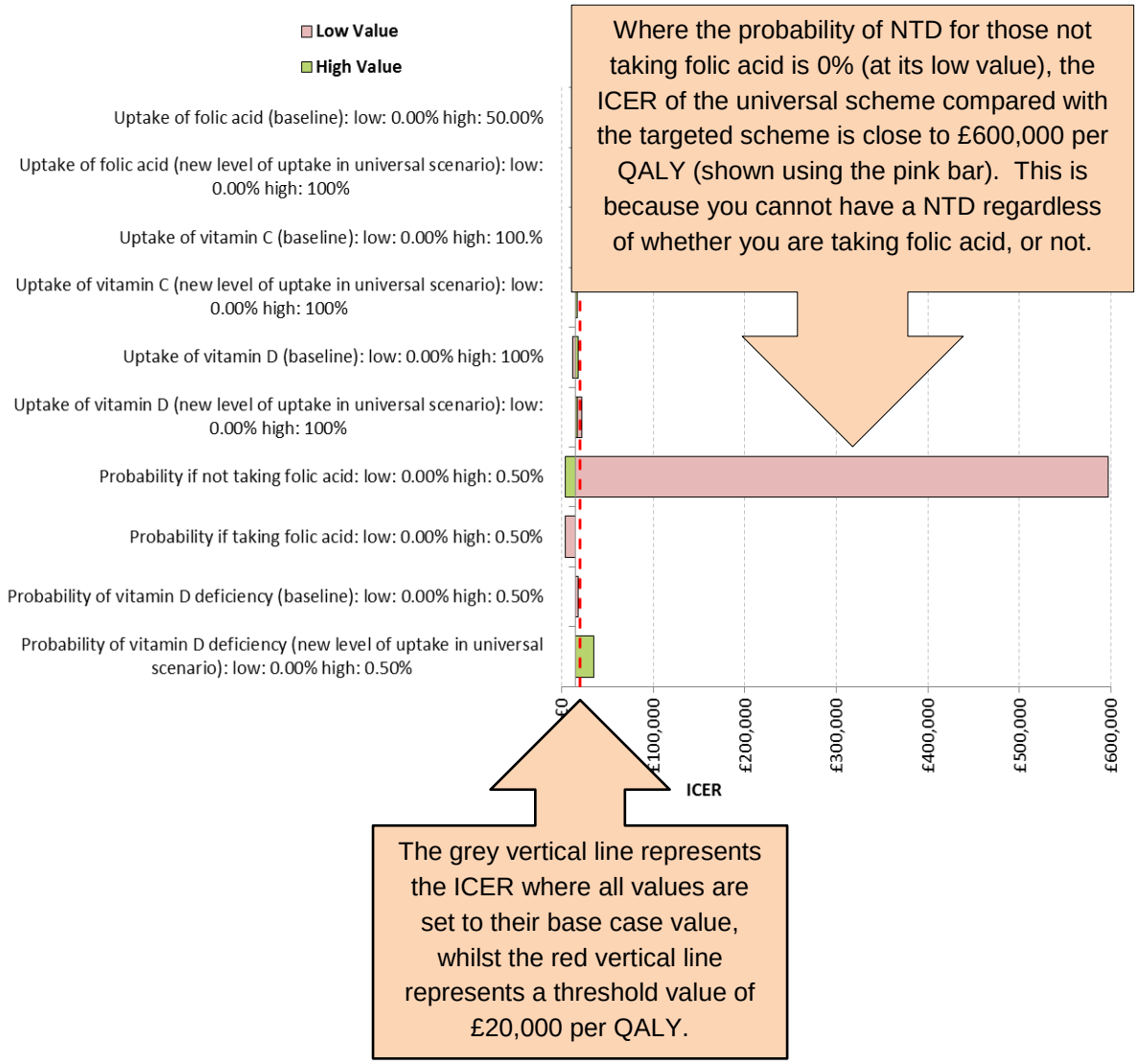
Within a tornado diagram, each model input parameter under consideration is varied between two plausible values, referred to as a 'high value' and a 'low value'. The 'high value' is the highest plausible value each input parameter can take, whilst the 'low value' is the smallest plausible value each input parameter can take. Figure C.1 shows how high and low values are displayed on a tornado diagram.

**Figure C.1: High and low input values**




The model is run using the high input parameter and an ICER generated. This is depicted on the tornado diagram with a green bar. The model is then run using the low input parameter and again an ICER is generated (shown with a pink bar). The green and pink bar combined represents the range of results that are generated using an input with two plausible, but extreme, values. This is displayed on Figure C.2.

**Figure C.2: Results of univariate sensitivity analysis**




Considering specifically "probability if not taking folic acid" in Figure C.2, shows that where this input is set to its highest plausible value, of 0.5%, the ICER is close to £0 per QALY (green bar). That is, where pregnant women who are not taking folic acid have a probability of a pregnancy affected by a NTD of 0.5% the universal scheme is cost-effective compared with the targeted scheme. This is because the increase in uptake of Healthy Start vitamin supplements resulting from the universal scheme has a relatively high scope for benefit, in that, pregnancies affected by a NTD can potentially be avoided in 0.5% of pregnancies. Conversely, the pink bar for "probability if not taking folic acid" on Figure C.2, shows that where the probability of NTD when not taking folic acid is 0%, the ICER is around £600,000 and thus the universal scheme would not be considered cost-effective compared with the targeted scheme. Where the baseline probability of NTD is at 0%, there is no scope for benefit from an increased uptake of Healthy Start vitamin supplements, i.e. the incidence of NTD cannot be reduced.

The change in ICER where the probability if not taking folic is varied is large, with ICERs generated of £0 per QALY to £600,000 per QALY. Therefore, this input has a large impact on the results of the model. Figure C.3 shows a full tornado diagram and can be used to show which inputs are driving the results, that is, which inputs when varied affect the model's results the most.

**Figure C.3: Full tornado diagram**

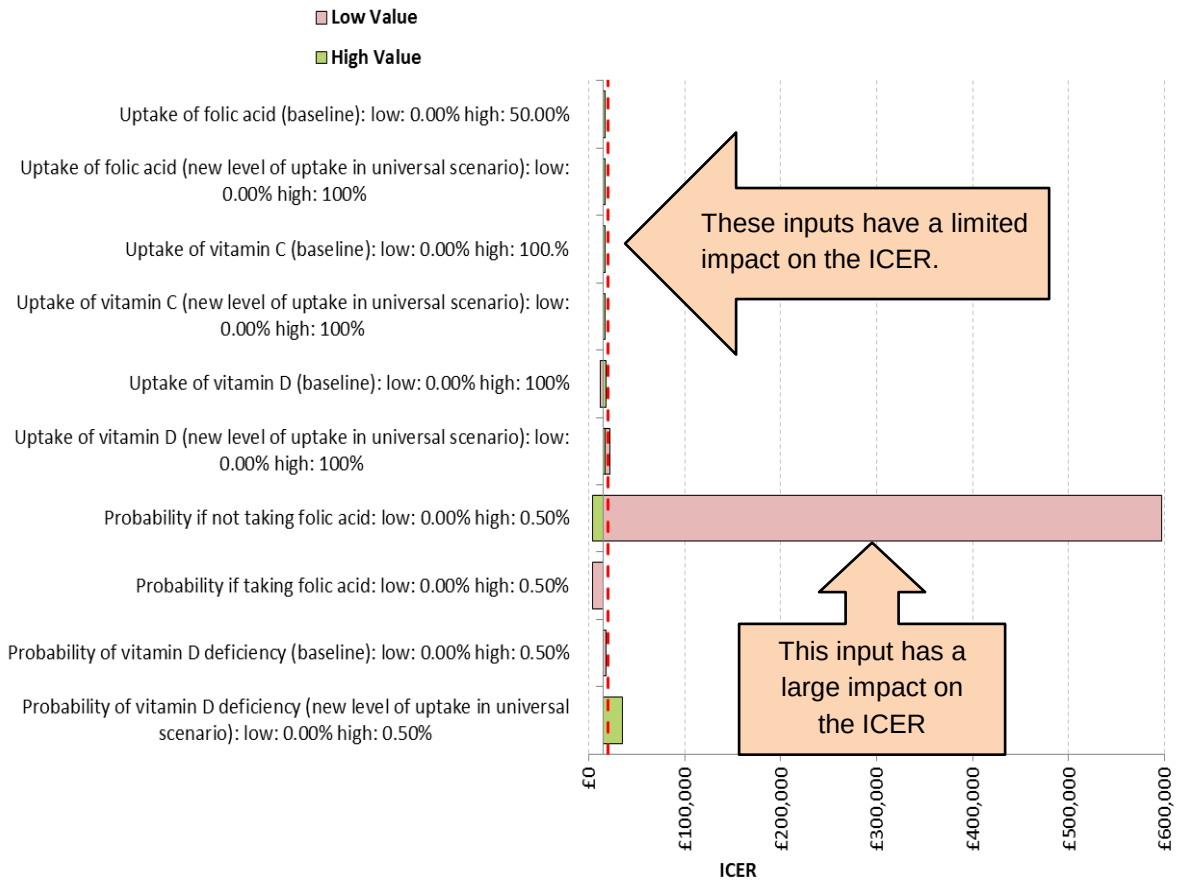



Figure C.3 can be interpreted in that those inputs with wider pink and green bars have a larger impact on results than those inputs with less wide bars. Therefore, it is apparent that the probability (of a pregnancy affected by a NTD) if not taking folic acid is clearly the key driver of the results for pregnant women after 10 weeks.