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ORIGINAL ARTICLE

Uptake of intra-muscular vitamin K administration after birth: A national cohort study

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Abstract

Aim: A long-acting monoclonal antibody against RSV (nirsevimab), given as an injection shortly after birth, is currently being rolled out globally. Carer acceptance of intra-muscular (IM) vitamin K, another injection given shortly after birth, could serve to indicate the acceptability of nirsevimab.

Methods: We analysed a national dataset of postnatal health visitor visits in Scotland; individual-level data on gestation were not available. The primary outcome measure was the modality of administration of vitamin K; potential explanatory variables were maternal age, infant ethnicity, English as a first language, and measures of socio-economic deprivation. We examined associations between IM vitamin K administration or oral/no vitamin K and each explanatory variable.

Results: From 2019 to 2021, questionnaires were available for 142 857 infants; data was missing for 2.7%. IM Vitamin K uptake was high: 95.5% of carers consented, with 1.1% requesting oral vitamin K and 0.9% refusing vitamin K altogether. Infant ethnicity, use of English as a first language, socio-economic status and maternal age were not associated with reduced uptake of IM vitamin K.

Conclusion: If IM Vitamin K administration is a valid proxy measure for nirsevimab acceptance, we did not identify groups that might require increased engagement prior to nirsevimab roll-out.

KEYWORDS
immunisation, intra-muscular, vitamin K

1 | INTRODUCTION

Following recent positive results for nirsevimab, a long-acting monoclonal against RSV, in randomised controlled trials,[1,2] it has been approved for use by the European Medicines Agency[3] and the Food and Drug Administration in the United States (US).[4] It is currently being used in Spain, France and the US,[5] and is likely to be rolled out in a larger number of countries in the near future. As a one-off injection of an intra-muscular (IM) agent potentially given shortly after birth, it bears more similarity to the routine administration of Vitamin K than to those of routine infant immunisations, which in the United Kingdom (UK) commence at the age of 2 months.[6]

In the UK, vitamin K can be administrated as an IM (routine administration) or an oral agent (which must be prescribed by a medical professional). A review found that carers who do not consent to

Abbreviations: IM, Intra-muscular; SIMD, Scottish Index of Multiple Deprivation; UK, the United Kingdom; US, the United States.

the administration of IM vitamin K, request oral vitamin K instead, or refuse all vitamin K, may do so for two broad reasons.[7] The first is due to concerns about the potential harm to an infant: the distress that injection for their newborn child may cause, or because of concerns that IM vitamin K may lead to an increased risk of leukaemia, a possibility raised in the 1990s[8] that was subsequently refuted by further research.[9,10] A second category of carers may desire their infants to have a more 'natural' neonatal course, driven either by religious beliefs or a belief that vitamin K deficiency is to be expected for infants.[7]

Previous studies have found conflicting relationships between carer demographics and refusal of IM vitamin K. A study from the United States showed that mothers who refused IM vitamin K were more likely to be of White ethnicity, aged >30 years, or college graduates[11]; however other studies found maternal non-white ethnicity to be a predictor for refusal of vitamin K.[12,13]

Decisions made about modality of vitamin K administration appear to be associated with subsequent choices about childhood immunisations. A study from the US found an association between the refusal of IM vitamin K and the refusal of other preventive measures, including the hepatitis B vaccine at birth, prophylaxis against gonococcal ophthalmia, and subsequent routine vaccination.[14] A study from New Zealand found that carers who declined vitamin K for their newborn infants were 14-fold more likely to not proceed with routine childhood immunisations, and those that opted for oral vitamin K were 3.5 times more likely to subsequently non-immunise.[12]

With this study we aimed to understand the uptake of IM vitamin K in infants in Scotland. In line with the previous literature, we hypothesised that there would be infant or maternal demographic variables that would be associated with reduced uptake of IM Vitamin K.

The rationale for the study was that the results, as well as being informative about the overall acceptability of an intervention such as nirsevimab, could inform decisions on which populations might need specific targeted interventions to boost uptake.

Key notes

- Carer acceptance of intra-muscular (IM) vitamin K might serve as a proxy measure for the acceptance of anti-RSV passive immunisation; little up-to-date data is available on IM vitamin K uptake.
- In a large national dataset we found high uptake of IM vitamin K, with no maternal or infant demographic variables associated with reduced uptake.
- Our findings should prove reassuring to clinicians and policy makers planning the roll-out of the passive immunisation for RSV.

2 | MATERIALS AND METHODS

2.1 | Dataset

All variables described below are collected as part of the Health Visitor First Visit Report, which is offered at the age of 10–14 days for all newborn infants in Scotland. Coverage of the health visitor first visit is high, with 97.3% of eligible children (those turning 10 days old) receiving a review in the period 2018–2021.[15] Data collected includes date of birth, address with postcode, gender, maternal age, and the first language used at home (Appendix S1). Data were analysed for infants born between 1 January 2018 and 31 December 2022. Specific ethical approval was not considered necessary as this study made use of existing aggregate population-level data, without any linkage or access to individual records. Individual level data on gestation at birth was not available as this is collected in a distinct national dataset (Scottish Morbidity Record 02).

2.2 | Variables collected

We collected information on the primary outcome measures of IM vitamin K administration, oral vitamin K administration, or no Vitamin K administration.

We also collected information on explanatory variables of maternal age (age bands <20, 20–24, 25–29, 30–34, 35–40 and >40), infant ethnicity (white Scottish, white other British, white Polish, white Other, Asian, Black Caribbean/African, Mixed/Multiple Ethnicity, and Other/Not Known), whether English was a first language at home (Yes/No) and Scottish Index of Multiple Deprivation (SIMD),[16] a relative measure of deprivation across 6976 small areas in Scotland called data zones (with a mean of 785 individuals per data zone in 2021), based on home postcode, grouped by quintile.

2.3 | Analysis

We first explored the patterns of missing recording of Vitamin K administration. We tested to see whether there were differences over time in the proportion of infants who received IM vitamin K, as there may have been behavioural differences before and after the Covid-19 pandemic. We used a Fisher's exact test to compare the proportion of infants who received IM vitamin K in 2018 and 2019 to subsequent years (2019–2021 and 2020–2021, respectively). We grouped together oral and no vitamin K administration as markers of IM vitamin K non-acceptance and compared this to IM vitamin K administration.

We then examined whether there were associations between IM vitamin K administration or oral/no vitamin K and each explanatory variable. We used a Fisher exact test for categorical variables that could be set out in a 2×2 contingency table (English as a first language at home), and Chi square testing for categorical variables with a larger number of variables (ethnicity, SIMD and maternal age). All analyses were implemented in RStudio and R version 4.2.2.[17] Other/Not Known ethnicity was excluded as this group was likely to be highly heterogenous. Missing/incomplete data was not included in

the analyses, and no imputation was made of missing data as this was unlikely to be missing randomly.

2.4 | Ethics

This analysis was undertaken on aggregate routinely-collected data obtained from Public Health Scotland via information request and released in accordance with PHS disclosure control procedures. More information on how PHS collects and processes health data is available via their privacy notice.[18]

3 | RESULTS

3.1 | Features of the dataset

Data were available for a total of 193 441 infants reviewed from 2018 to 2021 (Table 1). The percentage of newborns who received IM vitamin K increased from 93.7% in 2018 to 95.7% in 2021. The likelihood of IM vitamin K being administered increased from 2018 compared to subsequent years (2019–2021, OR 1.72, $p < 0.001$) but there was no further significant increase from 2019 onwards (OR of 1.03 for 2019 compared to 2020–2021, $p = 0.48$). Therefore subsequent analyses were conducted using the dataset from 2019 to 2021 (142 857 infants). This 2019–2021 dataset had low rates of missing or invalid data (2.7%) and overall 1.8% of carers opted for either oral vitamin K (1.1%) or no vitamin K (0.7%).

3.2 | Infant ethnicity and English as a first language in the home

Full data was available on ethnicity for 134 997 infants (94.5%) from 2019 to 2021 (Table 2). IM vitamin K non-acceptance was highest in the white Polish group (3.2% of those with data available opted for oral or no vitamin K) and lowest in the Black, African or Caribbean group (1.0% opted for oral or no vitamin K); however sample sizes were small both groups (2827 and 2270 infants respectively) and a chi-square test showed no evidence of a significant difference between the groups ($p = 0.23$).

Data were available on the first language used at home for 133 599 infants (93.5%). For those with English as a first language 1.8% opted for oral or no vitamin K, as opposed to 2.1% for those who did not state that English was their first language; this difference was not significant ($p = 0.06$).

3.3 | Area-level deprivation

Data was available on socioeconomic position categorised by SIMD quintile for 138 958 infants (97.2%). There was no clear association between socio-economic position and IM vitamin K acceptance (Table 3; $p = 0.22$).

TABLE 1 Vitamin K administration data for the period 2018–2021.

Vit K administration	2018 (%)	2019 (%)	2020 (%)	2021 (%)	Totals for 2019–2021 (%)
Intra-muscular	47 419 (93.7)	46 644 (95.1)	44 886 (95.7)	44 891 (95.7)	136 421 (95.5)
Oral	1086 (2.1)	569 (1.2)	542 (1.2)	514 (1.1)	1625 (1.1)
None	455 (0.9)	330 (0.7)	304 (0.6)	319 (0.7)	953 (0.7)
Missing/Invalid	1624 (3.2)	1527 (3.1)	1166 (2.5)	1165 (2.5)	3858 (2.7)
Total	50 584	49 070	46 898	46 889	142 857

TABLE 2 Vitamin K administration data for the period 2019–2021 by infant ethnicity.

Ethnicity	Oral/None (%)	IM (%)	Total
White	1903 (1.8)	104 323 (98.2)	106 226
White Other British	136 (1.9)	7034 (98.1)	7170
White Polish	91 (3.2)	2736 (96.8)	2827
White Other	164 (2.6)	6048 (97.4)	6212
Asian	116 (1.8)	6241 (98.2)	6357
Black, Caribbean or African	22 (1.0)	2248 (99.0)	2270
Mixed/Multiple ethnicity	81 (2.1)	3854 (97.9)	3935
Total	2513	132 484	134 997

Abbreviation: IM, intra-muscular.

TABLE 3 Scottish index of multiple deprivation status and vitamin K administration for the period 2019–2021.

SIMD Quintile	Oral/None (%)	IM (%)
Q1 (most deprived)	556 (1.7)	32 101 (98.3)
Q2	650 (2.3)	28 230 (97.7)
Q3	596 (2.3)	24 806 (97.7)
Q4	468 (1.6)	27 911 (98.4)
Q5 (least deprived)	308 (1.3)	23 332 (98.7)
Total	2578	136 380

Abbreviations: IM, intra-muscular; SIMD, Scottish Index of Multiple Deprivation.

TABLE 4 Maternal age and vitamin K administration for the period 2019–2021.

Maternal age	Oral/None (%)	IM (%)
<20	79 (2.3)	3404 (97.7)
20–24	382 (2.2)	17258 (97.8)
25–29	769 (2.1)	36665 (97.9)
30–34	745 (1.6)	46330 (98.4)
35–39	474 (1.7)	26698 (98.3)
40+	124 (2.0)	5940 (98.0)
Total	2573	136295

Abbreviation: IM, intra-muscular.

3.4 | Maternal age

Data were available on maternal age for 138868 infants (97.2%). The maternal age bands with the highest rates of IM vitamin K acceptance were 30–34 and 35–39. However absolute differences between the groups with the highest (<20 years; 2.3%) and lowest (30–34 years; 1.6%) rates of IM vitamin K non-acceptance was small (0.7%), and there was no significant difference between the age distributions of those who opted for oral or no vitamin K, and those who opted for IM administration ($p = 0.22$) (Table 4).

4 | DISCUSSION

Overall rates of IM vitamin K acceptance in this cohort were high, with only 1.8% of carers in this dataset opting for the oral administration of vitamin K (1.1%), or no vitamin K (0.7%). We did not find an association between baby ethnicity, English as a first language, socio-economic position as defined by SIMD quintile, maternal age, and IM vitamin K non-acceptance.

Our estimate is of 1.8% of carers in this dataset opting out of the recommended post-natal administration of IM vitamin K. These rates are higher than those from previous population-level studies in a high-income setting. A study analysed births in the province of Alberta in Canada in the period 2006–2012, where 0.72% of carers declined IM vitamin K for their newborn infant,[19] and another that examined IM vitamin K administration across the US in 2015 similarly found that 0.6% of carers of refused this.[13] However, the rates of vitamin K administration appear to be much lower in lower-income settings such as India, where 62.4% of newborns received this postnatally,[20] or Nepal, where only 17.1% of infants in government hospitals received vitamin K,[21] and therefore our findings are unlikely to be applicable to such settings, where systems and access factors are likely to have an influence as well as acceptability.

Strengths of our study include population level data for postnatal visits for infants born in all settings, very low rates of missing data, and up-to-date information on this intervention in a post-pandemic setting. The Scottish Child Health Surveillance Programme is unique in the UK for its coverage and completeness and therefore our findings are likely to be highly representative of the demographics of the births in this cohort during this time period.

Limitations include that this study was based on postnatal, aggregate data provided from the Child Health Surveillance Programme database by Public Health Scotland. Not all visits scheduled in the period 0–10 days take place, although in the period 2018–2021 97.3% of these did; infants likely not be included are those who are still in hospital at 10 days of age, or those whom the Health Visitor was unable to contact. IM vitamin K acceptance patterns in these groups (which is likely to include the most preterm infants, who are most likely to benefit from an intervention such as nirsevimab) may differ to those of the population as a whole.

In addition vitamin K IM acceptance profiles were not categorised according to birth location (home/birthing centre/hospital). A previous study from Tennessee in the US showed an association between delivery at home or at a midwife-led birthing centre and reduced rates of IM vitamin K acceptance, with up to 14.5% of carers opting out of IM vitamin K at home deliveries and 31% in birthing centres.[14] Birth centres and maternity wards in Scotland are commonly co-located on the same hospital site, and births coded by site rather than exact location of delivery, so this data was not available for this analysis. Home births are recorded in a separate birth dataset (National Records of Scotland) to that used for this study so again this data was not available for this analysis. Another limitation is that a high proportion of the mothers in this dataset self-reported white ethnicity (90.7%) and therefore these findings may not be applicable to other more ethnically diverse settings. Immunisation behaviours are known to differ between Scotland and adjacent England,[22] and therefore our findings may not necessarily be representative of the UK as a whole, or other high income settings.

Another limitation of our study is that we are unable to identify the exact proportion of infants born preterm in this cohort; this is the group most likely to benefit from any intervention such as nirsevimab. However, this dataset captured 97.3% of eligible births; in Scotland an estimated 8.2% of infants were born preterm in the period 2019–2021,[23,24] meaning that a proportion of the infants included in this dataset were born preterm, and provides reassurance that the findings don't apply to term-born infants only.

Our results support real world findings of the high acceptability and uptake of nirsevimab after birth in Galicia, Spain, with a recent paper showing uptake of 92.6% in infants born since the start of the immunisation campaign in September 2023.[25] A research priority in this patient population should be to identify groups with lower uptake, to identify possible interventions that might boost uptake and improve protection against severe RSV disease in this cohort.

5 | CONCLUSION

The rates of carer acceptance of an intra-muscular injection of IM vitamin K after birth were high in this national cohort. Infant ethnicity,

use of English as a first language at home, socio-economic status and maternal age were not associated with reduced uptake of IM vitamin K. If vitamin K is a valid proxy marker for acceptance of nirsevimab, then we did not identify any groups that might require increased engagement prior to the roll-out of the intervention.

AUTHOR CONTRIBUTIONS

Thomas C. Williams: Conceptualization; methodology; formal analysis; writing – original draft; writing – review and editing. **Susanne Brunton:** Data curation; formal analysis; writing – review and editing. **Lynda Fenton:** Conceptualization; writing – review and editing. **Pia Hardelid:** Conceptualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

All scripts and data produced are available online at https://git.ecdf.ed.ac.uk/twillia2/vitk_administration_scotland/.

ROLE OF THE FUNDER

The funder did not participate in the work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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