Endocrine Connections Publish Ahead of Print, published on September 18, 2017 as doi:10.1530/EC-17-0193

Title:

Variations in infant and childhood Vitamin D supplementation programs across Europe and factors influencing adherence

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Abstract: 250 **Manuscript**: 2772

Tables: 2 **Total figures: 3** **Colour figures: 2**

Abstract:

Background: Nutritional rickets is a growing global public health concern despite existing prevention programs and health policies. We aimed to compare infant and childhood vitamin D supplementation policies, implementation strategies and practices across Europe and explore factors influencing adherence.

Methods: European Society for Paediatric Endocrinology Bone and Growth Plate Working Group members and other specialists completed a questionnaire on country-specific vitamin D supplementation policy and child healthcare programs, socioeconomic factors, policy implementation strategies, and adherence. Factors influencing adherence were assessed using Kendall's tau-b correlation coefficient.

Results: Responses were received from 29 of 30 European countries (97%). Ninety-six per cent had national policies for infant vitamin D supplementation. Supplements are commenced on day 1-5 in 48% (14/29) of countries, day 6-21 in 48% (14/29); only the UK (1/29) starts supplements at 6 months. Duration of supplementation varied widely (6 months to lifelong in at-risk populations). Good (≥80% of infants), moderate (50-79%) and low adherence (<50%) to supplements was reported by 59% (17/29), 31% (9/29) and 10% (3/29) of countries, respectively. UK reported lowest adherence (5-20%). Factors significantly associated with good adherence were universal supplementation independent of feeding mode (p=0.007), providing information at neonatal unit (NNU) discharge (p=0.02), financial family support (p=0.005); monitoring adherence at surveillance visits (p=0.001) and the total number of factors adopted (p<0.001).

Conclusions: Good adherence to supplementation is a multi-task operation that works best when parents are informed at birth, all babies are supplemented and adherence monitoring is incorporated into child health surveillance visits. Implementation strategies matter for delivering efficient prevention policies.

Keywords: micronutrients, supplementation, fortification, policies, Europe, implementation

Introduction

Vitamin D deficiency and its complications such as osteomalacia, rickets, hypocalcaemic seizures, dilated cardiomyopathy and skeletal myopathy are a growing concern worldwide in high, medium and low income countries regardless of geographic location [1][2][3]. If left untreated, long-term morbidity includes leg deformities, muscle weakness, falls and fractures, disability, unemployment and early death, such as from cardiomyopathy or obstructed labour. The cause and effect relationship between vitamin D and bone health is well established [4]. Vitamin D supplementation of infants and pregnant mothers are practised in many countries to prevent rickets. The recent global consensus on the prevention of rickets recommends vitamin D supplementation not just during infancy and pregnancy but also for all ethnic risk groups (i.e. people with dark skin) especially those living at high latitude including all European countries [2][5]. In the wake of the European refugee crisis of 2015-2016, and the resulting longer term population demographic changes, Europe requires robust prevention programs to protect the most vulnerable [6]. However, there appears to be wide variation in the success of such vitamin D supplementation policies across Europe even for the existing population. We aimed to explore the differences in vitamin D policies and the factors relating to policy implementation that influence adherence rates.

Methods

A questionnaire with 20 questions was designed pertaining to the content of vitamin D supplementation policies, practices, infant health care and socioeconomic factors, and policy implementation strategies. The questions were based on expert opinion (from paediatric endocrinology and public health) of factors that were perceived to influence adherence to infant vitamin D supplementation. The questions entailed:

- Presence of a national policy and whether vitamin D supplementation was dependent on the mode of feeding;

- Time of commencement and duration of supplementation;
- Presence of a recommended number of child health surveillance visits and professionals providing care; Professionals responsible for prescribing vitamin D supplements
- Provision of financial family support and child care benefits by the government and whether supplements were free or paid for by the public;
- Whether adherence to supplementation is systematically monitored at child health surveillance visits and measured as part of national statistics. In the absence of national statistics, experts were asked to provide adherence rates for the first year of life from local audits or estimates, and details on adherence problems in certain sub groups of the population;
- Estimated average duration of breast feeding, and time of weaning; and
- Report of national policies on food fortification with vitamin D.

The questionnaire was sent to members of the European Society of Paediatric Endocrinology (ESPE) bone and growth plate working group in May 2014, which included representatives from Turkey, Israel and Russia. Additional effort was made, via various contacts and sources, to reach out to public health professionals and experts in the field in other European countries. Contacts were established with 30 countries and all except Iceland (97%) responded. For countries with two respondents, responses to dichotomous variables (yes/no) were only included if they were consistent. For countries with more than 2 respondents, the response of the majority was considered in the final analysis, when there was inconsistency in response. When adherence was provided as an estimated range, the highest quoted rate was used for statistical analysis.

Statistical analysis:

Descriptive statistics was used, and countries were ranked by adherence rate for the first year of life, as the main outcome. Countries were grouped into good (≥80% of infants), moderate (50-79%) and

low adherence (<50%). Adherence rate was cross tabulated with the total number of factors, and each individual factor, using Kendall's tau-b correlation coefficient in SPSS statistical software version 22.0. The effect of individual factors and the total number of factors (n=11) on estimated country-specific adherence rates was compared.

Results

Thirty-nine responses were received electronically from representatives of 29 European countries. Two responses were received from Poland, Portugal, Netherlands and Serbia, three from Spain and six from Germany.

Characteristics of National policies:

All countries except Italy (96%, 28/29) reported to have a national policy in place for vitamin D supplementation in infancy and childhood. Universal supplementation independent of the mode of feeding is recommended by 79% of countries (23/29) whereas only breast-fed infants are supplemented in Italy, Russia, Serbia, Greece and the UK (17%, 5/29).

Commencement and duration of supplementation:

Vitamin D supplementation is commenced from day 1-5 of life in 48% (14/29) and day 6-21 in 48% (14/29) of European countries; the UK is the only country (1/29) where supplements are not recommended until 6 months of life. The recommended duration of supplementation varied widely, ranging from a minimum of 6 months to lifelong in at risk population (Supplementary **Table 1**).

Professionals providing child health surveillance and prescribing vitamin supplements:

Information to new parents on the rationale for vitamin D supplementation is provided before discharge from the neonatal/delivery unit in 86% of countries (24/28). Albania, Spain, Greece and the

UK did not provide information to parents at discharge. Response from Portugal was not considered due to inconsistency.

All countries except Greece and Romania (93% of countries), have a recommended number of child health surveillance visits usually associated with immunization schedules ('red book' or passport programs). The various professionals providing child health surveillance are illustrated in **Figure 1a**. Paediatricians provide child health surveillance solely (41%) or in partnership with other health care professional (another 28%).

The responsibility of prescribing vitamin D is with the paediatrician in most countries, either solely (41%, 12/29) or in partnership with general practitioners (24%, 7/29); as illustrated in **Figure 1b.**

Financial family support and child benefits:

Patients pay for their prescription in 62% of countries (18/29) whereas governments provide free vitamin D supplies in 28% (8/29). In Italy and the UK, only families on low-income support receive free supplements and in Norway only people from ethnic minorities.

Financial family support for children is provided by 86% of countries (25/29), varying from birth to a minimum of 26 weeks and a maximum of 18 years; however only 28% of countries (7/25) - Albania, Austria, Bulgaria, France, Hungary, Italy and Macedonia - expect a 100% attendance at child health surveillance visits to be eligible to claim these benefits.

Adherence and monitoring:

All countries reported an adherence rate to infant vitamin D supplementation in the first year of life. Denmark, Turkey and Israel (11%) were the only countries that monitored adherence as part of national statistics. Germany, Ireland, Norway, Spain and UK provided evidence from regional studies. Estonia and Italy specified that the estimates were personal opinions and the remaining countries (19/29) did not specify the source of information and were assumed to be subjective estimates. Countries are ranked by adherence in **Table 2** and depicted in **Figure 2**. Good adherence (≥80% of

infants) was reported by 59% of countries (17/29), moderate adherence (50-79%) by 31% (9/29) and low adherence (<50%) by 10% of countries (3/29). The UK had, by far, the lowest adherence rate (5-20%). Poor adherence in specific population subgroups was reported by 46% (13/28) of countries; however subgroups were named only by 6 countries. Bulgaria, Norway, Romania, Serbia, Sweden and Switzerland specified compliance issues in Romani communities, 'non-Westerners', the rural population, immigrants, low socioeconomic groups and protestant sects, respectively.

led number of child health surveillance visits for on-going assessment of a child's growth and development are practised in 93% (27/29) of European countries, however only 67% (18/27) incorporate a monitoring check for adherence to vitamin D supplementation.

Infant feeding and food fortification:

Breast feeding was estimated to be practiced by >70% of mothers at 3 months and >50% at 6 months in 41% (12/29) of countries. Fewer women are breastfeeding in the other 59% of countries (17/29) - 10-70% of mothers at 3 months and 10-50% at 6 months.

Weaning is recommended at 6 months in 48% of countries (13/28) and 4 months in 25% of countries (7/28). The recommendations varied between 4-6 months in 25% of countries (7/28), mostly depending on mode of feeding. Estonia recommended weaning at 4 months for vegetables and 6 months for meat.

Voluntary fortification of foods, other than infant formula, with vitamin D is practised in 55% of countries (16/29). No European country, except Israel currently mandates fortification. Fortified foods included milk, margarine, yogurt, butter, dairy products, breakfast cereals, baby food and cookies.

Factors influencing adherence:

Factors significantly associated with good adherence were: universal supplementation independent of the mode of feeding (p=0.007), providing information on supplementation at discharge from neonatal units [NNU] (p=0.02), availability of financial family support (p=0.005), monitoring of adherence to

supplementation at child health surveillance visits (p=0.001) and the total number of factors adopted (p<0.001). Currently only 55% (16/29) of countries incorporate all the 4 significant individual factors.

The proportion of countries adopting each significant factor in the 3 adherence groups is illustrated in **Figure 3**. Countries with good adherence fulfilled 6-9 (median 8) of the 11 factors listed in **Table 2**, whereas countries with moderate and low adherence fulfilled between 3-7 (median 6) and 2-5 (median 5) factors, respectively.

Factors not significantly associated with adherence rate included: Presence of National vitamin D supplementation policy (p=0.4), commencement of supplements on day 1-5 (p=1.0), free vitamin D supply by the government (p=0.7), having a recommended number of child health surveillance visits (p=0.07), mandatory attendance at surveillance visits to claim benefits (p=0.1), National monitoring of adherence to supplementation (p=0.8) and fortification of food with vitamin D (p=1.0).

Discussion

This survey demonstrates that vitamin D supplementation policies, their implementation strategies and adherence vary widely across Europe. Our study shows that *universal vitamin D supplementation independent of the mode of feeding*, *providing information on supplementation at discharge from NNU, monitoring of adherence* at recommended child health surveillance visits and *availability of financial family support* are policy features and implementation strategies associated with good adherence. Adherence improved as the *total number of factors adopted* increased. Other factors, such as the cultural acceptance of supplements by different ethnic groups were reported, but could not be sufficiently explored.

Universal supplementation from early life (<21days of life), is currently practiced by 83% (24/29) of European countries. Vitamin D in infant formula is insufficient to protect infants from developing rickets [7]. Hence, the global consensus on the prevention of rickets [2][3] recommends 400 IU/day (10 μg) of vitamin D from birth to a minimum of 12 months of age, independent of the mode of feeding. This recommendation is also supported by our results, demonstrating that universal

supplementation is associated with good adherence. Since vitamin D deficiency in the mother is always passed on to the infant, and serum half-life of 25-hydroxy vitamin D (25OHD) is only 2 weeks, prevention of rickets must include supplementation of pregnant women, and infants from birth [2][3]. In the UK, supplements are not commenced until 6 months of age, which contributes to the rising incidence of rickets [8][9] the morbidity from hypocalcaemic seizures [10], the deaths from hypocalcaemic cardiomyopathy [11], and undiagnosed rickets found post-mortem after unexplained sudden infant deaths reported in this country [12][13]. Notably, the vast majority of infants in these UK studies were from dark-skinned ethnic origin, and fully breastfed. This study demonstrates that providing information at discharge from NNU and monitoring supplementation during health surveillance visits were associated with good adherence. Providing information and monitoring will automatically alert parents to the necessity of supplementation. Despite 93% (27/29) of countries having a recommended number of child health surveillance visits, only 70% (19/27) of these countries monitor adherence to vitamin D supplementation program at these visits. A survey from UK has demonstrated that 85% of parents are unaware of the need for infant vitamin D supplementation [16] possibly due to lack of monitoring and lack of information at discharge from NNUs. Ultimately, for supplementation policies to work, healthcare professionals should be responsible for prescribing and monitoring, which is best done alongside recommended health surveillance visits and immunisation schedules, and documented in the personal child health record (‘red book’ or passport). Similarly, supplementation during pregnancy can be easily monitored during routine visits using the antenatal health record or passports.

Financial family support significantly enhanced adherence, and should therefore be incorporated into policies where feasible. Whilst strict implementation of a free, monitored vitamin D supplementation programme reduced the prevalence of rickets in Turkey [17], this study found that free, unmonitored vitamin D supply in isolation did not increase adherence, a finding supported by the low uptake of ‘Healthy Start’ free vitamins in the UK [18]. Although promotion campaigns reportedly reduce the incidence of symptomatic vitamin D deficiency [19][20], monitoring of supplementation at recommended health surveillance visits is a more sustainable and systematic way of ensuring

awareness and adherence, according to this study. We also demonstrate that policy implementation is a multi-task operation. The more factors incorporated into policies, the greater the adherence.

High-risk populations (reduced sunlight exposure due to geographic location, covered clothing, dark skin, institutionalisation or hospitalisation and low socio-economic status, reduced dietary calcium intake) should receive vitamin D supplementation beyond 12 months of age [2][3], which is currently not universally practised in Europe. The incidence of rickets [5] and prevalence of symptomatic [21][22][23][24] and simple vitamin D deficiency in Europe [25] is several folds higher in dark-skinned (resident or immigrant) ethnic sub-groups compared to white children. Ethnic minority and immigrant children remain at increased risk of symptomatic vitamin D deficiency beyond the recommended age of supplementation as demonstrated in the UK [24][26] and Denmark [27]. These countries have changed their policies recommending lifelong supplementation in risk groups [15][27]. Similarly, the high prevalence of undiagnosed osteomalacia in adults related to vitamin D deficiency [28] highlights the importance of lifelong supplementation in the high risk population. In light of the migration of dark skinned people into Europe, there is an urgent need to review vitamin D supplementation policies and their implementation. Increased incidence of rickets in the immigrant population has been attributed not only to dark skin pigmentation, sun avoidance, covering the skin, but also low dietary calcium intake [5]. Of note, Norway and Sweden reported poor adherence in the immigrant population, and Romania and Serbia in those with low socio-economic status, a known risk factor for poor adherence [29]. Public health policies should therefore provide monitored, universal supplementation of all infants and these risk groups (dark-skinned, low-socio economic status).

Food fortification of appropriate foods in conjunction with supplementation is most effective in preventing vitamin D deficiency by increasing serum population 25OHD levels [30] as seen in Canada [31]. The majority of European countries in this study follow voluntary fortification, as noted before [32], and countries tend to fortify milk and milk products. Limiting fortification to one food type may put certain groups at risk [33], therefore it is essential to consider dietary habits of at risk populations and target fortification accordingly [34].

Vitamin D status in children is poorly studied across the globe [35]. Paucity of National data on adherence to prevention programs, as highlighted here, creates challenges in designing and comparing prevention policies. Policy makers should consider a central European database which holds information on health policies to enable information retrieval and update. The EURopean micronutrient RECommendations Aligned (EURRECA), established to address differences between countries in micronutrient recommendations may be the right platform [36]. Availability of accurate statistics on adherence will provide more robust evidence required to influence legislative authorities. In addition, investing in the prevention of vitamin D deficiency seems to have significant economic benefits [37][38][39].

The main study limitation was that information on adherence, feeding practises and non-adherent groups was mainly based on expert opinions. In addition, some inconsistent responses where noted when there was more than one respondent, which may reflect regional differences within countries. However, in the absence of national data, estimation by experts in the field was the next best alternative. Data from 22 European countries were missing because no contact could be established. Nonetheless, the largest western and central European countries are represented (55%), with different cultural and economic backgrounds.

Conclusion

The rise in nutritional rickets and low adherence to vitamin D supplementation are major public health concerns. Whilst national supplementation policies are in place across Europe, their implementation has been somewhat neglected. The results of this survey demonstrate that relatively simple implementation strategies are associated with good adherence. Apart from providing information at discharge from NNU and universal supplementation of all babies, independent of the mode of feeding, the results of this survey specifically suggest that integrating the monitoring of adherence to supplementation into existing prevention programs such as the child health surveillance visits ('red book', passports) increases adherence. Providing financial family support also enhanced adherence, suggesting that incentivising parents can improve child health. Improving adherence is a multi-task operation and one should adopt as many factors as feasible. Low and moderate adherence countries should consider adopting successful implementation strategies from high adherence European countries.

We call for more political effort to invest in implementation of efficient supplementation and fortification programmes to prevent symptomatic vitamin D deficiency, and thereby protect the most vulnerable members of society, and minimise inequalities among socioeconomic groups and ethnic minorities.

Key points:

- All infants, pregnant women and risk groups should receive preventative vitamin D supplements.
- Supplementation policies are failing due to lack of clear implementation strategies and responsibilities.
- 59% of European countries have good adherence to supplementation during the first year of life. Adherence to supplementation in the UK is lowest in Europe.
- Monitoring adherence at child health surveillance visits, providing universal supplementation and financial family support are factors significantly associated with good adherence.
- A policy is only as good as its implementation strategy. Low and moderate adherence countries should consider adopting successful implementation strategies from high adherence European countries.

List of collaborators: We would like to thank all the clinicians and contributors who kindly completed the questionnaire

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Serap Turan & Abdullah Bereket

Nick Shaw & Eleanor McGee

Acknowledgement:

We would like to thank Peter Nightingale, statistician, University Hospital Birmingham, for excellent statistical support.

Conflict of interest: The authors have no conflict of interest.

Authorship statement:

SU- Acquisition, analysis and interpretation of data. Draft and critical revision of manuscript

AK- Acquisition of data

TT- Critical contribution from public health perspective

MA- Contribution from public health economic perspective

WH- Conception, design and data acquisition. Critical revision for intellectual content and final approval of manuscript.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Ethics: The study did not involve any human subjects therefore approval was not sought. As there were no patients involved consent was not obtained.

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Figure 1: Professionals responsible for providing child health surveillance (1a) and for prescribing vitamin D supplements (1b).

Fig 1a: Child health surveillance is provided by paediatricians in 41% of countries (12/29), followed by a combination of a paediatrician and a general practitioner (GP) in 21% (6/29). In Romania, Ireland, Hungary and Sweden, GPs provide health surveillance (14%, 4/29). Health visitors provide health surveillance in conjunction with: a Youth doctor in Netherlands, Paediatrician in Israel and GP in Denmark, Norway, Estonia and Finland (14%, 4/29). The UK is the only country where health surveillance is provided solely by health visitors.

Fig 1b: Vitamin D supplements are prescribed by the paediatrician in majority of the countries followed by a combination of paediatrician and general practitioner (GP). In Denmark, vitamin D is prescribed by the health visitor, in Sweden by the 'well baby clinic', in Israel by the 'Mother and Child Health centre', in Netherlands by the health visitor (HV) or 'Mother and Child Health centre'. Vitamins are not prescribed but available to buy over the counter in Finland and Ireland. In Estonia and Norway, vitamin D is prescribed by GP or HV whereas in Lithuania and Romania, it is prescribed by the GP.

Figure 2: Adherence rates for infant vitamin D supplementation in the first year of life in Europe. In the absence of national statistics the adherence rates given are subjective estimates by experts in the field. Good adherence (≥80% of infants supplemented) is indicated in green, moderate adherence (79-50%) in orange and low adherence (<50%) in red.

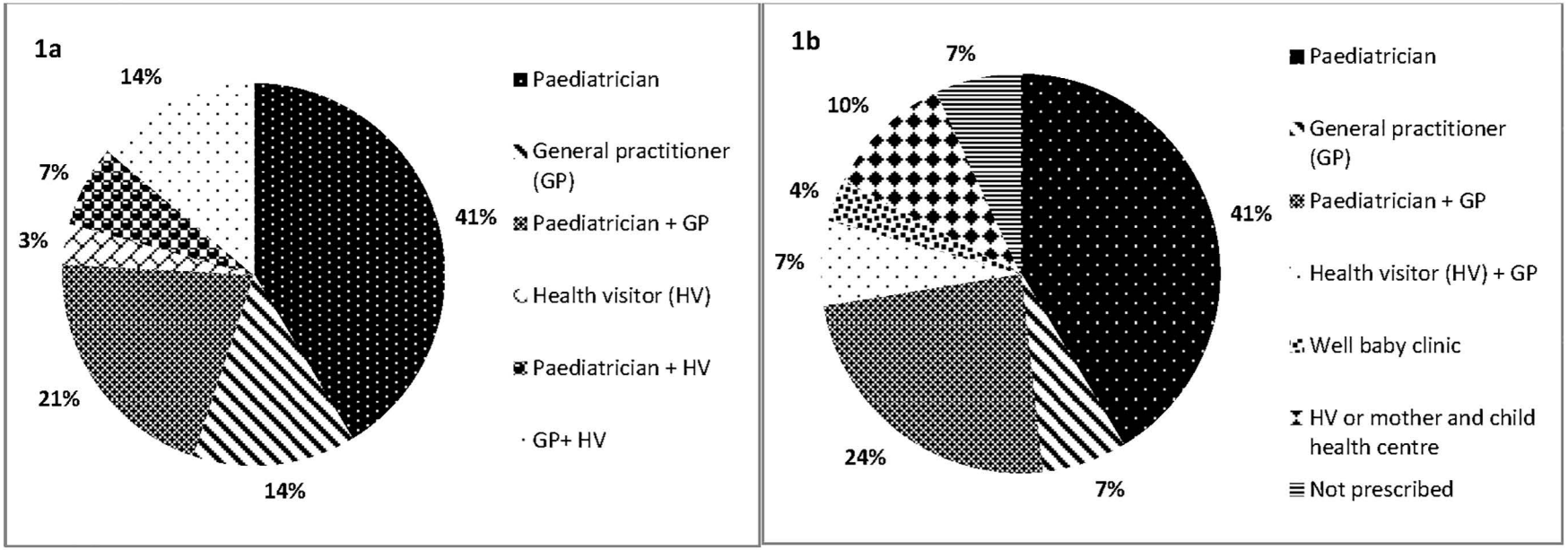
Figure 3: Percentage of countries adopting each of the 4 independent significant factors, per adherence groups. Good ≥ 80%, moderate 50-79% and low < 50% of infants supplemented during the first year of life.

Table 2: Summary of national infant vitamin D supplementation policies ranked by adherence rates in different European countries. Factors significantly associated with adherence are highlighted.

Country	Adherence rate	National policy	Universal supplementation	Vit D started on day 1-5	Information at NNU discharge	Free supply	Financial family support	Child health surveillance	Monitoring adherence at surveillance	Mandatory surveillance visits to claim benefit	National monitoring adherence	Food Fortification	Total number of factors
Austria	98%	√	√	√	√		√	√	√	√			8
Hungary	98%	√	√		√		√	√	√	√		√	8
Israel	80-97%	√	√	√	√		√	√	√		√	√	9
Czech Republic	95%	√	√	√	√	√	√	√	√				8
Netherlands	90-95%	√	√		√		√	√	√			√	7
Sweden	90%	√	√		√	√	√	√	√			√	8
France	90%	√	√	√	√	√	√	√		√		√	9
Estonia	90%	√	√		√	√	√	√	√			√	8
Lithuania	90%	√	√		√		√	√	√				6
Macedonia	90%	√	√	√	√		√	√	√	√			8
Germany	70-90%	√	√	√	√	√	√	√	√				8
Belgium	70-90%	√	√	√	√		√	√	√			√	8
Finland	85%	√	√		√		√	√	√			√	7
Russia	80%	√			√		√	√	√			√	6
Turkey	80%	√	√	√	√	√	√	√	√		√		9
Albania	80%	√	√			√	√	√	√	√		√	8
Bulgaria	70-80%	√	√		√		√	√		√			6
Norway	75%	√	√		√	√*	√	√	√			√	8
Romania	70%	√	√	√	√	√	√						6
Switzerland	70%	√	√	√	√		√	√					6
Poland	65-70%	√	√	√	√		√	√				√	7
Denmark	60-70%	√	√		√		√	√	√		√		7
Portugal	50-70%	√	√				√	√	√				5
Italy	50-60%			√	√	√*		√		√			5
Spain	50- 64%	√	√					√					3
Ireland	59%	√	√	√	√		√	√	√			√	8
Serbia	45%	√		√	√			√				√	5
Greece	30%	√										√	2
UK	20%	√				√*	√	√				√	5

√* Free only for certain groups

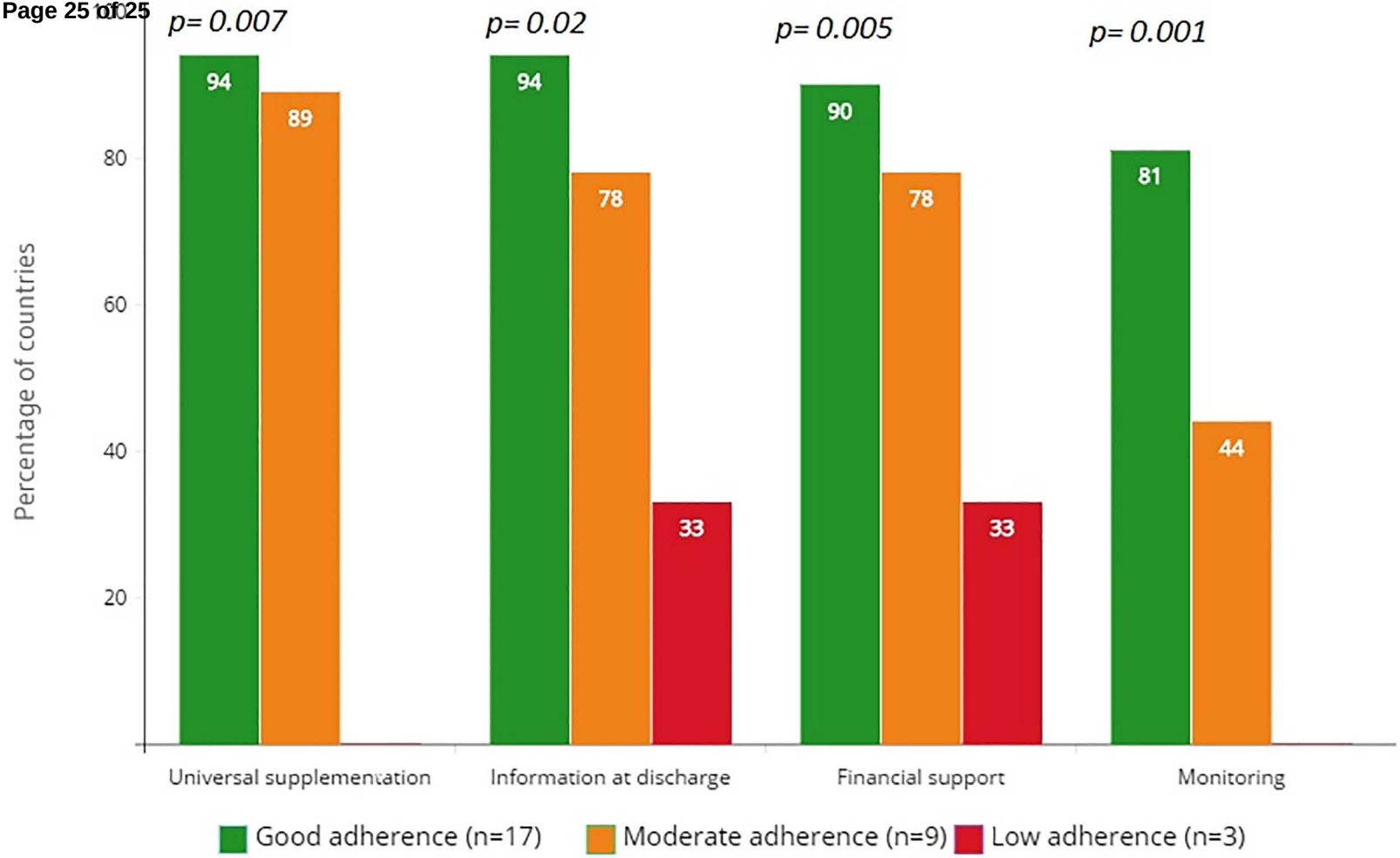
Figure 1: Professionals responsible for providing child health surveillance (1a) and for prescribing vitamin D supplements (1b).



Adherence to vitamin D supplements in the first year of life

- Low adherence
- Moderate adherence
- Good adherence

90%
80%
85%
75%
90%
60-70%
90%
59%
5-20%
65-70%
90-95%
70-90%
70-90%
95%
98%
98%
90%
70%
70%
50-60%
45%
70-80%
90%
80%
80%
30%
50-70%
50-64%
80-97%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p= 0.005
p= 0.001
94
89
94
78
33
90
78
33
81
44
100
80
60
40
20
Percentage of countries
Universal supplementation
Information at discharge
Financial support
Monitoring
Good adherence (n=17)
Moderate adherence (n=9)
Low adherence (n=3)