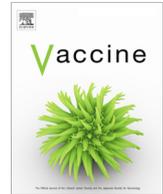




Contents lists available at ScienceDirect

## Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)

## Linking cohort data and Welsh routine health records to investigate children at risk of delayed primary vaccination



Suzanne Walton<sup>a</sup>, Mario Cortina-Borja<sup>a</sup>, Carol Dezateux<sup>b</sup>, Lucy J. Griffiths<sup>a,c</sup>, Karen Tingay<sup>d</sup>, Ashley Akbari<sup>c,e</sup>, Amrita Bandyopadhyay<sup>c,f</sup>, Ronan A. Lyons<sup>c,e</sup>, Richard Roberts<sup>g</sup>, Helen Bedford<sup>a,\*</sup>

<sup>a</sup> Population, Policy and Practice Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, London, WC1N 1EH, UK

<sup>b</sup> Centre for Primary Care, Wolfson Institute of Population Health, Queen Mary University of London, E1 2AB, UK

<sup>c</sup> Population Data Science, Administrative Data Research UK, Swansea University, Wales, SA2 8PP, UK

<sup>d</sup> Office for National Statistics, Cardiff Road, Newport, NP10 8XG, UK

<sup>e</sup> Population Data Science, Health Data Research UK, Swansea University, Swansea, SA2 8PP, UK

<sup>f</sup> Population Data Science, National Centre for Population Health and Wellbeing Research, Swansea University Medical School, Swansea, SA2 8PP, UK

<sup>g</sup> Public Health Wales, 2 Capital Quarter, Tyndall Street, Cardiff, CF10 4BZ, UK

### ARTICLE INFO

#### Article history:

Received 15 March 2022

Received in revised form 13 June 2022

Accepted 28 June 2022

Available online 13 July 2022

#### Keywords:

Vaccination

Timeliness

DTP vaccine

Child

Millennium Cohort Study (MCS)

Child health systems

### ABSTRACT

**Background:** Delayed primary vaccination is one of the strongest predictors of subsequent incomplete immunisation. Identifying children at risk of such delay may enable targeting of interventions, thus decreasing vaccine-preventable illness.

**Objectives:** To explore socio-demographic factors associated with delayed receipt of the Diphtheria, Tetanus and Pertussis (DTP) vaccine.

**Methods:** We included 1,782 children, born between 2000 and 2001, participating in the Millennium Cohort Study (MCS) and resident in Wales, whose parents gave consent for linkage to National Community Child Health Database records at the age seven years contact. We examined child, maternal, family and area characteristics associated with delayed receipt of the first dose of the DTP vaccine.

**Results:** 98.6% received the first dose of DTP. The majority, 79.6% ( $n = 1,429$ ) received it on time (between 8 and 12 weeks of age), 14.2% ( $n = 251$ ) received it early (prior to 8 weeks of age) and 4.8% ( $n = 79$ ) were delayed (after 12 weeks of age); 1.4% ( $n = 23$ ) never received it. Delayed primary vaccination was more likely among children with older natural siblings (risk ratio 3.82, 95% confidence interval (1.97, 7.38)), children admitted to special/intensive care (3.15, (1.65, 5.99)), those whose birth weight was > 4Kg (2.02, (1.09, 3.73)) and boys (1.53, (1.01, 2.31)). There was a reduced risk of delayed vaccination with increasing maternal age (0.73, (0.53, 1.00) per 5 year increase) and for babies born to graduate mothers (0.27, (0.08, 0.90)).

**Conclusions:** Although the majority of infants were vaccinated in a timely manner, identification of infants at increased risk of early or delayed vaccination will enable targeting of interventions to facilitate timely immunisation. This is to our knowledge the first study exploring individual level socio-demographic factors associated with delayed primary vaccination in the UK and demonstrates the benefits of linking cohort data to routinely-collected child health data.

© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Delay in receiving scheduled vaccinations not only leaves individual children vulnerable to vaccine-preventable diseases but may also compromise herd immunity. Delayed primary vaccina-

tion has been found to be one of the strongest predictors of subsequent incomplete immunisation [1,2]. In the United States, infants who received the first dose of Diphtheria, Tetanus and Pertussis (DTP) vaccine on time were twice as likely to be up-to-date by two years of age; those not initiating their immunisations on time were two to three times more likely to be delayed for other immunisations given prior to two years of age [3]. Children who remain unimmunised or incompletely immunised with primary vaccines are also more likely not to receive measles, mumps and rubella vaccine (MMR) [4] or the pre-school boosters [5,6]. Identifying and

\* Corresponding author at: Children's Health, Population, Policy and Practice Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK.

E-mail address: [h.bedford@ucl.ac.uk](mailto:h.bedford@ucl.ac.uk) (H. Bedford).

addressing factors associated with delayed primary vaccination may improve vaccine timeliness, as well as overall vaccine uptake.

Although patterns of vaccination timeliness have been investigated, less research has focussed on factors associated with late receipt of vaccination. Factors associated with adherence to vaccination schedules are complex and context specific [7] and can be different for delayed compared with incomplete vaccination [8]. Delayed vaccination has been associated with factors indicative of lower socioeconomic status [2,8–13], race and ethnicity [8,12], residential mobility and medical conditions in the child [11]. In Scotland, using a population database containing immunisation records for over one million children, Friederichs found late MMR vaccination to be associated with deprivation, while the most affluent tended to be vaccinated promptly, or not at all [14]. Also, in Scotland, Haider et al [13] found associations between deprivation, uptake and timeliness for four childhood vaccines. Using data for nine London health service areas from the Child Health Information System, Tiley et al [15] reported that although the overwhelming majority of children were vaccinated on time, this was less likely for some ethnic minority groups.

There is limited information about other factors associated with delayed primary vaccination in a UK setting needed to facilitate targeting of interventions.

Delayed vaccinations may suggest broader lack of engagement with health services. In the USA, Rodewald found that among disadvantaged populations, delay in receiving vaccinations was associated with low uptake of other preventive health care services [16]. If this were also the case in the UK, then identification and targeting of those who are likely to delay vaccinations may also increase attendance for other child health promotion activities such as routine health and development reviews offered as part of the Child Public Health Programme [17].

This study builds on our earlier research describing the uptake and timeliness of vaccinations amongst Millennium Cohort Study (MCS) participants living in Wales [18]. The rich socio-demographic data gathered in the MCS, linked to electronic vaccination records provides a valuable opportunity to characterise children at risk of delayed vaccination. This will facilitate improved targeting of vaccination services. This cohort of children received separate DTP, polio, and *Haemophilus influenzae* type b (Hib) vaccines rather than the pentavalent vaccine (DTaP/IPV/Hib) introduced in 2004. We focus on the DTP vaccine as it was closest to the hexavalent vaccine (DTaP/IPV/Hib/HepB) used currently in the UK. This study explored socio-demographic factors associated with delayed receipt of the DTP vaccine.

## 2. Methods

### 2.1. Study population

We analysed a subset of data from the MCS, a UK-wide nationally representative birth cohort [19] comprising 18,818 children from 18,552 families born between September 2000 and January 2002. Parents were interviewed at home when their child was aged nine months and subsequently at three, five, seven, eleven and fourteen years of age. At the age seven home visit, written consent was sought from parents to link MCS information collected until each child's 14th birthday, to data routinely collected by government departments or agencies, and other public sector organisations. The Northern and Yorkshire Research Ethics Committee approved the MCS age seven survey; no additional approval was needed for this linked data analysis, which focusses on those resident in Wales. Our target population was singletons resident in Wales, whose natural mothers took part in the first interview. Parents of 1,840 (94.3%) of 1,951 singletons resident in Wales, con-

sented to health record linkage. Linked MCS and National Community Child Health Database (NCCHD) records were available for 1,831 children. We excluded 46 children interviewed in countries other than Wales on one or more occasions by age eleven years and three for whom the main respondent was not the natural mother at the first interview, leaving a final sample of 1,782.

### 2.2. Record linkage

We accessed coded data from the NCCHD, which brings together data from centrally coordinated but locally administered child health system databases held by NHS organisations and includes information from birth registrations, child health examinations and vaccinations.

We used the privacy-protecting trusted research environment in Wales known as the Secure Anonymised Information Linkage (SAIL) Databank to store and access our data. Datasets imported into SAIL are anonymised and linked using a split file process preventing access to both identifiable data and clinical information at the same time. Records are linked through assigning unique encrypted Anonymised Linkage Fields (ALF) to person-based records [20]. Additional information on linkage and linkage rates for this project has been published elsewhere [21].

### 2.3. Timeliness of vaccination

Children born in Wales between August 2000 and November 2001 should have received the DTP vaccine at 8, 12 and 16 weeks of age and a booster dose between the age of three years and four months and five years. Consistent with our earlier methodology [18], the first dose of the DTP vaccine was considered to be delayed if it was received when the child was over 12 weeks of age.

To reduce deductive disclosure, each child's date of birth was supplied by SAIL as the week of birth (set to the Monday), and a day of birth within that week was assigned by adding a uniform random number between 0 and 6 days. Age at vaccination was calculated using this assigned date and the actual date of vaccination from NCCHD records.

### 2.4. Potential factors associated with delayed vaccination

As little is known about socio-demographic factors associated with delayed primary vaccinations in the UK, we explored factors associated with wider vaccination outcomes, such as uptake or delay, reported both in the UK and internationally [5–8,22–30]. These included a range of child, maternal, family and area characteristics obtained from MCS data collected at the nine months interview (Table 1).

### 2.5. Statistical Methods

All analyses were performed using StataSE 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) Survey and non-response weights at age seven years were used to adjust for clustered sampling design, data missing due to losses to follow-up, and lack of consent to linkage [31,32]. Weighted percentages were calculated and reported.

As overdispersion was not present, Poisson Regression models were fitted to explore associations with delayed receipt of DTP. As the outcome of interest was delayed vaccination, those ( $n = 23$ ) who had no record of being vaccinated with DTP (up to fourteen years of age) were grouped with those who had received the vaccine early or on-time. Any factors with global significance ( $\text{Prob} > F$ ) of  $p < 0.1$  in the univariable Poisson regressions were included in a multivariable Poisson regression model following a

**Table 1**  
Variables included in the analysis.

<b>Child</b>	
Sex	Female Male
Prematurity	Term / Preterm (<37 weeks)
Birth weight (Kg)	<2.5Kg 2.51 to 3 Kg 3.01 to 3.5Kg 3.51 to 4Kg >4 Kg
Admitted to special / neonatal intensive care	Yes
Number of hospital admissions	No 0 / 1 / 2 or more
Birth order	1 2 or more First born (first live birth) Not First born (has older natural siblings)
<b>Family / Household</b>	
Total number of children in the household	1 2 or 3 4 or more
Paternal employment	In work or on leave Not in work or on leave
Housing tenure	Own or mortgage Rent Living elsewhere
Household income per annum	£0.00 to <£10,400 £10,400 to <£20,800 £20,800 to <£31,200 £31,200 to <£52,000 £52,000 and above
Income weighted quintile	Lowest quintile (lowest income) Second quintile Third quintile Fourth quintile Highest quintile
<b>Mother</b>	
Age at birth of child (years)	Per 5 year increase
Socio-economic status	Mangement & professional Intermediate Small employer & self-employed Lower supervisory & technical Semi-routine & routine Never employed
Employment status	In work Not in work
Academic qualifications	Degree Diploma / A levels O level / GCSE Other None
Smoking during pregnancy	No or gave up during pregnancy Yes
Whether breastfed baby	Ever Never
Marital / partnership status	Legally separated Married (first and only marriage) Remarried (second or later marriage) Single (never married) Divorced or widowed
Longstanding illness	Yes No
<b>Area</b>	
Ward type	Advantaged Disadvantaged
Living area	Urban Rural

step-wise model selection strategy. Factors were kept in the final multivariable model if  $p \leq 0.05$ .

We conducted a sensitivity analysis to assess whether using Monday (first day in the assigned week of birth) or Sunday (last day in week in the assigned week of birth) as opposed to assigning a random day within the week, altered the conclusions made.

### 3. Results

Of the 1,782 children in this analysis, 919 (51.6%) were boys; the majority (97.2%) was from a white ethnic background. At the first MCS interview, 1,233 (69.2%) lived in ‘disadvantaged’ and 549 in ‘advantaged’ electoral wards, with 1,350 (75.8%) living in urban and 432 in rural areas. (‘Disadvantaged’ electoral wards were Electoral Divisions existing in 1998 that fell into the top part of the Child Poverty Index and ‘advantaged’ wards were those not in the top part of the Child Poverty Index. Disadvantaged wards were oversampled [31], but the weights were adjusted in analyses making results nationally representative).

In total, 98.6% ( $n = 1,759$ ) of children received the first dose of DTP; with the majority 79.6% ( $n = 1,429$ ) receiving it between 8 and 12 weeks of age, 14.2% ( $n = 251$ ) early (before 8 weeks of age), 4.8% ( $n = 79$ ) late (over 12 weeks of age) and 1.4% ( $n = 23$ ) with no record of receipt by 14 years of age [18].

The number of children categorised as receiving DTP defined as late was 111, 64 and 79 when the day of birth was assigned to a Monday, Sunday or Thursday respectively. We explored associations with key variables using the different days and did not find any consistent differences in outcomes (data not shown). We chose to use the random day of birth for consistency with our earlier work and to reduce misclassification bias.

Delayed DTP vaccination (Table 2) was associated with characteristics of the child, mother and household. In the unadjusted analysis, delay was more likely for boys than girls (risk ratio 1.57 (95% CI 1.01, 2.44)), babies with older natural siblings (2.61 (1.55, 4.40)), those admitted to special or intensive care following delivery (2.24 (1.10, 4.57)) and babies whose birth weight was >4Kg (1.95 (1.03, 3.69)). DTP vaccination was more likely to be delayed in children whose mothers had no academic qualifications (1.70 (1.04, 2.78)), were not in employment (2.25 (1.37, 3.67)), who smoked during the pregnancy (1.90 (1.08, 3.34)) and who did not breast feed (2.18 (1.27, 3.77)). Household factors found to be significantly associated with delayed DTP vaccination included a larger number of children in the household (for four or more children (4.55 (2.35, 8.81))), low household income and income quintile, housing tenure (renting a property (2.13 (1.24, 3.65))) and the mother’s partner not being in work (2.21 (1.15, 4.24)).

In the final adjusted model (Table 2), children with older natural siblings were nearly four times as likely to have delayed DTP vaccination than those who were first born (risk ratio 3.82 (95% CI 1.97, 7.38)). Delay was more likely among children admitted as a baby to special/intensive care (3.15 (1.65, 5.99)), among boys (1.53 (1.01, 2.31) and among babies with a birth weight of over 4 Kg (2.02 (1.09, 3.73)). The risk of vaccine delay decreased with increasing maternal age (0.73 (0.53, 1.00) per 5-year increase) and maternal education to degree level (0.27 (0.08, 0.90)). Associations were also seen with specific categories of maternal social class and household income quintile, but there were no consistent trends.

### 4. Discussion

This study shows that whilst the majority of infants were vaccinated in a timely manner, delayed primary vaccination was more likely among children with older natural siblings, those admitted to special or intensive care following delivery, those whose birth weight was >4Kg and boys. There was a reduced risk of delayed

**Table 2**  
Factors associated with late receipt of the first DTP vaccine.

Measure		Weighted % late (no.)	Unadjusted RR (95% CI)	p-value	Prob > F	Adjusted RR (95% CI)	p-value
Maternal age at child's birth - per 5 year increase			0.78 (0.60–1.00)	0.053	0.0525	0.73 (0.53–1.00)	0.053
Maternal academic qualifications	Degree	1.2% (265)	0.23 (0.07–0.72)	0.012	0.0109	0.27 (0.08–0.90)	0.034
	Diploma / A levels	2.4% (309)	0.46 (0.20–1.03)	0.060		0.54 (0.21–1.43)	0.21
	O level / GCSE	5.3% (867)	1			1	
	Other	3.6% (23)	0.68 (0.12–4.02)	0.67		0.60 (0.10–3.51)	0.56
	None	8.9% (316)	1.70 (1.04–2.78)	0.035		1.49 (0.90–2.46)	0.12
Maternal social class	Mangement & professional	2.7% (467)	1		0.0000	1	
	Intermediate	5.8% (283)	2.17 (0.95–4.96)	0.067		1.13 (0.48–2.65)	0.77
	Small employer & self-employed	0.0% (64)	n/a	<0.0001		n/a	<0.0001
	Lower supervisory & technical	2.4% (114)	0.89 (0.23–3.46)	0.86		0.30 (0.07–1.37)	0.12
	Semi-routine & routine	5.5% (707)	2.07 (0.97–4.39)	0.058		0.62 (0.28–1.38)	0.24
	Never employed	10.1% (125)	3.79 (1.73–8.29)	0.001		0.94 (0.35–2.49)	0.89
Maternal work status	In work / on leave	3.0% (920)	1		0.0016		
	Not in work / on leave	6.7% (862)	2.25 (1.37–3.67)	0.002			
Smoked during pregnancy	No or gave up	3.9% (1295)	1		0.0257		
	Yes	7.4% (487)	1.90 (1.08–3.34)	0.026			
Whether breastfed	Ever	3.3% (1083)	1		0.0056		
	Never	7.1% (699)	2.18 (1.27–3.77)	0.006			
Sex	Female	3.7% (863)	1		0.0454	1	
	Male	5.8% (919)	1.57 (1.01–2.44)	0.045		1.53 (1.01–2.31)	0.047
Birth weight	<2.5Kg	6.0% (90)	1.44 (0.63–3.29)	0.38	0.0725	0.83 (0.34–1.92)	0.66
	2.51 to 3 Kg	3.7% (277)	0.87 (0.39–1.95)	0.74		0.91 (0.43–1.94)	0.80
	3.01 to 3.5Kg	4.2% (693)	1			1	
	3.51 to 4Kg	4.8% (513)	1.14 (0.55–2.36)	0.73		1.14 (0.58–2.23)	0.71
	>4 Kg	8.2% (206)	1.95 (1.03–3.69)	0.040		2.02 (1.09–3.73)	0.025
Admitted to special / neonatal intensive care	No	4.4% (1636)	1		0.0271	1	
	Yes	9.8% (145)	2.24 (1.10–4.57)	0.027		3.15 (1.65–5.99)	0.001
Birth order	First born	2.5% (751)	1		0.0005	1	
	Has older natural siblings	6.6% (1031)	2.61 (1.55–4.40)	<0.0001		3.82 (1.97–7.38)	<0.0001
Total number of children in HH	1	2.5% (748)	1		0.0001		
	2 or 3	6.0% (921)	2.37 (1.38–4.07)	0.002			
	4 or more	11.5% (1113)	4.55 (2.35–8.81)	<0.0001			
Household income per annum	£0.00 to <£10,400	6.2% (493)	0.94 (0.56–1.55)	0.79	0.0279		
	£10,400 to <£20,800	6.6% (587)	1				
	£20,800 to <£31,200	1.2% (342)	0.18 (0.06–0.50)	0.001			
	£31,200 to <£52,000	2.9% (224)	0.44 (0.13–1.47)	0.18			
	£52,000 and above	2.3% (60)	0.35 (0.08–1.50)	0.15			
Income weighted quintile	Lowest quintile (lowest income)	6.9% (445)	1		0.0007	1	
	Second quintile	6.2% (403)	0.90 (0.49–1.65)	0.72		1.07 (0.55–2.08)	0.83
	Third quintile	5.9% (355)	0.86 (0.54–1.37)	0.52		1.25 (0.70–2.23)	0.45
	Fourth quintile	0.5% (318)	0.07 (0.02–0.22)	<0.0001		0.15 (0.04–0.51)	0.003
	Highest quintile	2.9% (261)	0.43 (0.17–1.08)	0.071		0.82 (0.33–2.06)	0.68
Housing tenure	Own or mortgage	3.4% (1090)	1		0.0133		
	Rent	7.2% (602)	2.13 (1.24–3.65)	0.007			
	Living elsewhere	5.1% (90)	1.51 (0.56–4.07)	0.41			
Whether partner is in work	In work / on leave	4.0% (1255)	1		0.0185		
	Not in work / on leave	8.8% (178)	2.21 (1.15–4.24)	0.019			

RR - Risk Ratio

Missing Values: Maternal academic qualifications 2; Maternal social class 22; Birth weight 3; Admission to SCBU 1; Household income 76; Partner in work 349

vaccination with increasing maternal age and for babies born to graduate mothers.

To our knowledge this is the first study linking data from a nationally representative cohort study with routine health records to explore factors associated with delayed primary vaccinations in a UK setting. The high consent rate to link vaccination records, which provide accurate vaccination histories, with the rich data in the MCS enabled us to explore associations between vaccine delay and a range of socio-demographic factors. However, as the study was based on Welsh participants in the MCS who had not been interviewed outside Wales at any of the MCS sweeps, we were unable to explore potential associations with UK country or residential mobility in and out of Wales. We were also unable to explore associations with maternal and child ethnicity, first language and language spoken at home because of small numbers

from minority ethnic groups in the study population. At present due to lack of a unified child health database in England, it is not possible to easily replicate this analysis for the UK as a whole.

We did not have access to the children's actual dates of birth to calculate ages at vaccination. However, using the random day within the week of birth should not have affected the proportions reported as early, on-time or delayed [33]. Ideally children should have received the first dose of the DTP vaccine as close to 8 weeks of age as possible. In the absence of an official definition of delay, we chose to define it according to the time the second vaccine was due. Although, using the random day of birth will have resulted in some misclassification of those who were and were not delayed based around the 12 weeks of age cut-off point, the random nature of this misclassification, should have prevented bias in our findings but may have weakened some of the associa-

tions reported for factors associated with vaccination delay. Furthermore, we tested alternative strategies for assigning day of birth in a sensitivity analysis and these did not materially affect our findings.

Our analysis compared children with vaccination delay against those who received the vaccine on-time, early or not at all (up to the age of 14 years). At the time when primary vaccinations are due and interventions can be applied, healthcare professionals won't know which group children will ultimately end up in, but if they are aware of factors associated with delay, it may give them the opportunity to target those children. We accept that this approach may have weakened some of the associations.

The majority of children in this cohort were immunised on time. However, consistent with other studies from many countries, children with older siblings were nearly four times as likely to have delayed DTP vaccination, than first born children [7,9]. This may reflect challenges accessing services as a result of competing demands on parents' time, making attending appointments difficult or decreased parental worry [34]. Babies who had been admitted to a special or intensive care following delivery were more than three times likely to be delayed receiving their first DTP vaccination. We did not have data on babies' length of stay in special care units, but some may have been hospitalised for significant periods of time and opportunities for timely vaccination in hospital may have been missed. Babies admitted to special care units are likely to have conditions that make them not only more likely to catch a vaccine preventable disease, but to be more vulnerable to the effects of the disease and so are in particular need of protection by vaccination. Vaccination may be delayed because health professionals or parents incorrectly believe vaccination is contraindicated [35]. On discharge, even after a short hospital stay, parents of these children experience stress which may persist [36] and once home, over-protective parents may delay attending routine appointments including for vaccination; vaccinations may not be prioritised in discharge plans and parents may delay vaccinations so their child can 'have a rest' after discharge [37]. In contrast with some studies, we did not find an association between prematurity and vaccination delay [35]; indeed a review by Sisson et al, shows a lack of consensus on effects of hospitalisation on vaccination timeliness for preterm or low birth weight infants [38]. Although studies have shown that hospitals do not always use opportunities to immunise older children [39,40], hospital based immunisation initiatives have been shown to be effective in ensuring preterm babies are immunised on time [41]. We are unable to explain our finding that boys were more likely to have delayed vaccination than girls, although similar unexplained associations have been found in other studies. In a 1993 study in Liverpool, parents of boys were less likely to consent to pertussis vaccine than parents of girls [42]. More recently and also using MCS data, Pearce et al found that girls were less likely to be unimmunised against MMR at age three years than boys [30]. Both these observations were made in the years following vaccine safety controversies. Our finding that heavier babies were more likely to have delayed vaccination is unexplained, although as higher birth weight is associated with complicated deliveries and conditions notably gestational diabetes, delayed attendance for vaccination may result from poorer maternal health status.

Consistent with other studies, the risk of vaccine delay decreased with increasing maternal age [23,43] and delay was associated with lower maternal academic qualifications [8]. Associations were seen with specific categories of maternal social class and household income quintile, but there was no consistent trend with these factors as a whole. Other studies [13,44,45] using either the Welsh or Scottish Index of Multiple Deprivation have found that associations between deprivation and vaccination uptake

and timeliness increase with the age of the child and number of vaccine doses.

Our analysis was not based on a current cohort of children and hence the estimates of delayed vaccination may not reflect the current picture. Similarly, our focus was on DTP vaccine, which is now given as part of a hexavalent vaccine DTaP/IPV/Hib/HepB (6-in-1) introduced in UK in 2017. In 2009 NICE published guidance on improving vaccine uptake [46]. Although we have described the characteristics of the children in whom immunisation was delayed and of their families, we are unable to explore whether the reasons for delay were intentional or not. In the USA, Smith found that 21.8% of parents reported intentionally delaying vaccinations for their children (aged 19 to 35 months). Of these, 44.8% did so because of concerns about vaccine safety or efficacy and 36.1% delayed because of an ill child [47]. However more recently Homel et al [11] reported parental attitudes contributed a relatively small percentage of delay. Our findings would suggest that in this cohort, delay arose from the complexities of life arising from social disadvantage, busy lives with large families and babies requiring special care and this is borne out by other studies. Recently there has been intense focus on the issue of 'vaccine hesitancy' a term used to refer to a "delay in acceptance or refusal of vaccination despite availability of vaccination services" [48] with suggestions that vaccine hesitancy is increasing, however, since data are not routinely gathered on timeliness of vaccination in the UK, it is not possible to comment on whether delay in vaccination, one element of vaccine hesitancy, has increased.

We consider that socio-demographic factors associated with delay in vaccination are unlikely to have altered significantly and these findings provide insights into where efforts to improve vaccine timeliness should be best targeted. To monitor this in future we would suggest routine assessment of vaccination timeliness.

Delayed receipt of the first dose of primary immunisations has been found to predict subsequent incomplete immunisation. Therefore, improving the timeliness of the first dose may improve both timeliness of subsequent doses and of completed courses of vaccination and thus vaccine uptake rates. This study assists in identifying those groups of infants who are at increased risk of delayed vaccination. In the absence of national data on vaccination timeliness, awareness of factors associated with delay may allow targeted interventions for those at highest risk. For infants admitted to a special or intensive care this could include offering vaccination prior to discharge or ensuring that appropriate communication takes place with their General Practitioner for vaccination in the community. Provision of clear, easy to read information, with flexible and easy to access services may facilitate vaccination of infants growing up in large families or where there are competing demands on parents' time. Opportunistic catch-up during routine contact with health professionals would also reduce the inequalities that exist. More widely, this study underlines the importance of maternal education in facilitating positive health outcomes for children.

#### 4.1. Conclusions

This study demonstrates the benefits of using rich cohort data linked to routine child health data and to our knowledge, is the first study exploring socio-demographic factors associated with delayed receipt of primary immunisations, within a UK setting. Timely immunisation is important to provide children with maximum protection against serious infectious diseases.

##### Authors' contributions

HB and SW conceived and designed the study. KT, AB, LG, SW and AA were responsible for data curation. SW carried out the data analysis with support from HB and MC-B. SW and HB wrote the manuscript and all authors contributed to critically appraising

and review of the manuscript. All authors approved the final manuscript.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Acknowledgements

The authors are grateful to the Centre for Longitudinal Studies, UCL Institute of Education and the UK Data Service as well as the child health offices who enter data and NHS Wales Digital Health and Care Wales (DHCW), formerly known as the NHS Wales Informatics Service (NWIS) that maintain the CCH2000 CHIS system and central data record, who provide anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank, which is part of the national e-health records research infrastructure for Wales. This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank. We would like to acknowledge all the data providers who make anonymised data available for research. All research conducted has been completed under the permission and approval of the SAIL independent Information Governance Review Panel (IGRP) project number 0410.

### Funding

This work was supported by the Wellcome Trust (grant number 087389/B/08/Z). LG, CD, RAL and AA are supported by Health Data Research UK (HDR-9006), which is funded by the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, National Institute for Health Research (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation and Wellcome. RAL is also funded by the Asthma UK Centre for Applied Research (AUKAC-2012-01). KT was supported by an ESRC award establishing the Administrative Data Research Centre Wales (ES/L007444/1). AA, AB, LG and RAL are supported by the ADR Wales programme of work. The ADR Wales programme of work is aligned to the priority themes as identified in the Welsh Government's national strategy: Prosperity for All. ADR Wales brings together data science experts at Swansea University Medical School, staff from the Wales Institute of Social and Economic Research, Data and Methods (WISERD) at Cardiff University and specialist teams within the Welsh Government to develop new evidence which supports Prosperity for All by using the SAIL Databank at Swansea University, to link and analyse anonymised data. ADR Wales is part of the Economic and Social Research Council (part of UK Research and Innovation) funded ADR UK (grant ES/S007393/1). CD is supported by Barts Charity (Grant/Award Number: MGU0419). The Millennium Cohort Study [<http://dx.doi.org/10.14301/llcs.v7i4.410>] is funded by grants to the Centre for Longitudinal Studies at the Institute of Education from the Economic and Social Research Council and a consortium of government departments. Research at the UCL Institute of Child Health and Great Ormond Street Hospital for Children receives a proportion of the funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

### References

- [1] Petousis-Harris H, Grant CC, Goodyear-Smith F, Turner N, York D, Jones R, et al. What contributes to delays? The primary care determinants of immunisation timeliness in New Zealand. *J. primary health care*. 2012;4(1):12–20.
- [2] Bobo JK, Gale JL, Thapa PB, Wassilak SG. Risk factors for delayed immunization in a random sample of 1163 children from Oregon and Washington. *Pediatrics* 1993;91(2):308–14.
- [3] Guyer B, Hughart N, Holt E, Ross A, Stanton B, Keane V, et al. Immunization coverage and its relationship to preventive health care visits among inner-city children in Baltimore. *Pediatrics* 1994;94(1):53–8.
- [4] Pearce A, Elliman D, Law C, Bedford H. Does primary immunisation status predict MMR uptake? *Arch. Dis. Child*. 2009;94(1):49–51.
- [5] Tung S, Pearce A, Bedford H. Factors determining uptake of the pre-school booster vaccine: findings from the UK Millennium Cohort Study. *Arch. Dis. Child*. 2012;97(Suppl 1):A64–5.
- [6] Evans MR, Thomas DR. A retrospective cohort study of risk factors for missing preschool booster immunisation. *Arch. Dis. Child*. 1998;79(2):141–4.
- [7] Taui MC, Sato APS, Waldman EA. Factors associated with incomplete or delayed vaccination across countries: A systematic review. *Vaccine*. 2016;34(24):2635–43.
- [8] Dombkowski KJ, Lantz PM, Freed GL. Risk factors for delay in age-appropriate vaccination. *Public health reports (Washington, DC : 1974)*. 2004;119(2):144–55.
- [9] Moore HC, Fathima P, Gidding HF, de Klerk N, Liu B, Sheppard V, et al. Assessment of on-time vaccination coverage in population subgroups: A record linkage cohort study. *Vaccine*. 2018;36(28):4062–9.
- [10] Luman ET, McCauley MM, Stokley S, Chu SY, Pickering LK. Timeliness of childhood immunizations. *Pediatrics* 2002;110(5):935–9.
- [11] Homel J, Edwards B. Factors associated with delayed infant immunization in a nationally representative cohort study. *Child Care Health Dev*. 2018;44(4):583–91.
- [12] Hull BP, McIntyre PB. Timeliness of childhood immunisation in Australia. *Vaccine*. 2006;24(20):4403–8.
- [13] Haider EA, Willocks LJ, Anderson N. Identifying inequalities in childhood immunisation uptake and timeliness in southeast Scotland, 2008–2018: A retrospective cohort study. *Vaccine*. 2019;37(37):5614–24.
- [14] Friederichs V, Cameron JC, Robertson C. Impact of adverse publicity on MMR vaccine uptake: a population based analysis of vaccine uptake records for one million children, born 1987–2004. *Arch. Dis. Child*. 2006;91(6):465–8.
- [15] Tiley KS, White JM, Andrews N, Ramsay M, Edelstein M. Inequalities in childhood vaccination timing and completion in London. *Vaccine*. 2018;36(45):6726–35.
- [16] Rodewald LE, Szilagyi PG, Shih T, Humiston SG, LeBaron C, Hall CB. Is underimmunization a marker for insufficient utilization of preventive and primary care? *Arch. Pediatr. Adolesc. Med*. 1995;149(4):393–7.
- [17] Shribman S, Billingham K. Healthy Child Programme - Pregnancy and the first five years of life. Department of Health 2009.
- [18] Walton S, Cortina-Borja M, Dezateux C, Griffiths LJ, Tingay K, Akbari A, et al. Measuring the timeliness of childhood vaccinations: Using cohort data and routine health records to evaluate quality of immunisation services. *Vaccine*. 2017;35(51):7166–73.
- [19] Connelly R, Platt L. Cohort Profile: UK Millennium Cohort Study (MCS). *Int. J. Epidemiol*. 2014;43(6):1719–25.
- [20] Lyons RA, Jones KH, John G, Brooks CJ, Verplancke JP, Ford DV, et al. The SAIL databank: linking multiple health and social care datasets. *BMC Med. Inf. Decis. Making* 2009;9:3.
- [21] Tingay KS, Bandyopadhyay A, Griffiths L, Akbari A, Brophy S, Bedford H, et al. Record linkage to enhance consented cohort and routinely collected health data from a UK birth cohort. *Int. J. Population Data Sci*. 2019;4(1):579–89.
- [22] Pearce A, Mindlin M, Cortina-Borja M, Bedford H. Characteristics of 5-year-olds who catch-up with MMR: findings from the UK Millennium Cohort Study. *BMJ open*. 2013;3(7).
- [23] Samad L, Tate AR, Dezateux C, Peckham C, Butler N, Bedford H. Differences in risk factors for partial and no immunisation in the first year of life: prospective cohort study. *BMJ (Clinical research ed)*. 2006;332(7553):1312–3.
- [24] Walsh S, Thomas DR, Mason BW, Evans MR. The impact of the media on the decision of parents in South Wales to accept measles-mumps-rubella (MMR) immunization. *Epidemiol. Infect*. 2015;143(3):550–60.
- [25] Vandermeulen C, Roelants M, Theeten H, Depoorter AM, Van Damme P, Hoppenbrouwers K. Vaccination coverage in 14-year-old adolescents: documentation, timeliness, and sociodemographic determinants. *Pediatrics* 2008;121(3):e428–34.
- [26] Sandford H, Tata LJ, Browne I, Pritchard C. Is there an association between the coverage of immunisation boosters by the age of 5 and deprivation? An ecological study. *Vaccine*. 2015;33(9):1218–22.
- [27] Samad L, Butler N, Peckham C, Bedford H. Incomplete immunisation uptake in infancy: maternal reasons. *Vaccine*. 2006;24(47–48):6823–9.
- [28] Pearce A, Elliman D, Bedford H, Law C. Residential mobility and uptake of childhood immunisations: findings from the UK Millennium Cohort Study. *Vaccine*. 2008;26(13):1675–80.
- [29] Crocker J, Porter-Jones G, McGowan A, Roberts RJ, Cottrell S. Teenage booster vaccine: factors affecting uptake. *J. public health (Oxford, England)*. 2012;34(4):498–504.

- [30] Pearce A, Law C, Elliman D, Cole TJ, Bedford H. Factors associated with uptake of measles, mumps, and rubella vaccine (MMR) and use of single antigen vaccines in a contemporary UK cohort: prospective cohort study. *BMJ (Clinical research ed)*. 2008;336(7647):754–7.
- [31] Plewis I. *The Millennium Cohort Study: Technical Report on Sampling*. 4th Edition. Centre for Longitudinal Studies; 2007.
- [32] Sera F, Griffiths L, Dezateux C, Cortina-Borja M. Technical report on the enhancement of Millennium Cohort Study data with linked electronic health records; derivation of consent weights 2017.
- [33] Bandyopadhyay A, Tingay K, Akbari A, Griffiths L, Cortina-Borja M, Bedford H, et al. Integrating electronic health records from different sources across the UK: lessons from a record linkage study. *Int. J. Population Data Sci.* 2018;3(2).
- [34] Schaffer SJ, Szilagyi PG. Immunization status and birth order. *Arch. Pediatr. Adolesc. Med.* 1995;149(7):792–7.
- [35] Slack MH, Thwaites RJ. Timing of immunisation of premature infants on the neonatal unit and after discharge to the community. *Communicable disease and public health / PHLS.* 2000;3(4):303–4.
- [36] Al Maghaireh DF, Abdullah KL, Chan CM, Piau CY, Al Kawafha MM. Systematic review of qualitative studies exploring parental experiences in the Neonatal Intensive Care Unit. *J. Clin. Nurs.* 2016;25(19–20):2745–56.
- [37] Tillmann BU, Tillmann HC, Nars PW, Weber P. Vaccination rate and age of premature infants weighing <1500 g: a pilot study in north-western Switzerland. *Acta paediatrica (Oslo, Norway : 1992)*. 2001;90(12):1421–6.
- [38] Sisson H, Gardiner E, Watson R. Vaccination timeliness in preterm infants: an integrative review of the literature. *J. Clin. Nurs.* 2017.
- [39] Walton S, Elliman D, Bedford H. Missed opportunities to vaccinate children admitted to a paediatric tertiary hospital. *Arch. Dis. Child.* 2007;92(7):620–2.
- [40] Allen L, Vickerstaff H, Collinson A. Vaccine-preventable disease susceptibility in a British paediatric assessment unit. *Journal of Infection Prevention.* 2014;15(6):230–3.
- [41] Crawford NW, Barfield C, Hunt RW, Pitcher H, Buttery JP. Improving preterm infants' immunisation status: a follow-up audit. *J. Paediatr. Child Health* 2014;50(4):314–8.
- [42] Pearson M, Makowiecka K, Gregg J, Woollard J, Rogers M, West C. Primary immunisations in Liverpool. I: Who withholds consent? *Arch. Dis. Child.* 1993;69(1):110–4.
- [43] Curran D, Terlinden A, Poirrier JE, Masseria C, Krishnarajah G. Vaccine Timeliness: A Cost Analysis of the Potential Implications of Delayed Pertussis Vaccination in the US. *Pediatr. Infect. Dis. J.* 2016;35(5):542–7.
- [44] Roberts RJ, McGowan A, Cottrell S. Measuring inequalities in immunization in Wales and the impact of interventions. *Human Vaccines & Immunotherapeutics.* 2016;12(10):2704–6.
- [45] Perry M, McGowan A, Roberts R, Cottrell S. Timeliness and equity of infant pertussis vaccination in wales: Analysis of the three dose primary course. *Vaccine.* 2020;38(6):1402–7.
- [46] National Institute for Health and Care Excellence. *Immunisations: reducing differences in uptake in under 19s*. 2009.
- [47] Smith PJ, Humiston SG, Parnell T, Vannice KS, Salmon DA. The association between intentional delay of vaccine administration and timely childhood vaccination coverage. *Public health reports (Washington, DC : 1974)*. 2010;125(4):534–41.
- [48] MacDonald NE. Vaccine hesitancy: Definition, scope and determinants. *Vaccine.* 2015;33(34):4161–4.