Co-administration of routine paediatric vaccines in England often deviates from the immunisation schedule

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ABSTRACT

Vaccine co-administration can facilitate the introduction of new vaccines in immunisation schedules and improve coverage. We analysed real life data to quantify the extent of routine paediatric vaccine co-administrations as recommended and as never recommended in the immunisation schedule in England, and assessed factors for recommended and never recommended vaccine co-administrations.

Immunisation data for all scheduled routine paediatric vaccines between 2008 and 2018 was obtained from the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC).

We included 6257,827 doses administered to 1,005,827 children. Twenty-one percent of vaccines were given separately, 79% were co-administered. Sixty-four percent of vaccines scheduled for co-administration were co-administered as recommended while 15% were administered separately. Among all vaccine co-administrations, 75% happened as recommended in the schedule, 4% were never recommended, while 21% deviated from the schedule. Vaccine co-administration according to the schedule varied greatly between vaccines. Forty-eight percent of English children received at least one of their vaccine co-administrations not as recommended in the immunisation schedule, with 19% of children receiving none of their co-administered vaccines as recommended. Late administration of one or more vaccines increased the odds for deviated co-administrations (OR 1.60) and strongly increased the odds for never recommended co-administrations (OR 5.34). Differences between genders, NHS regions, and IMD quintiles were statistically significant but small.

Suboptimal co-administration rates for routine paediatric vaccines are a missed opportunity and should be optimised by concerted public health action.

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Introduction

Vaccine co-administrations can be useful to introduce new vaccines in immunisation schedules and to maximise coverage, including facilitated catching-up for missed doses [1–6]. Co-administration may also improve adherence to immunisation schedules (i.e., timeliness) and minimise physician visits [7]. Thus, it is more cost-effective than giving each vaccine alone [5,8].

In 2018, the NHS paediatric routine immunisation schedule recommended six co-administrations [9]. Co-administrations are developed to assure optimal protection against vaccinepreventable diseases while minimising potential side effects [10,11]. However, adherence to crowded immunisation schedules may not always be possible and the timing of vaccinations may be shifted for various reasons. This may lead to delays and unscheduled co-administrations. Such unscheduled co-
administrations of vaccines, particularly when off-label, may lead to interference and potentially alter their efficacy and safety profiles [12,13].

Studies investigating vaccine co-administration typically document schedule feasibility [2,3], often to inform programme introduction. Studies assessing adherence to vaccination schedules typically evaluate programme implementation and coverage without much attention to co-administration specifically [14]. We analysed to which extent routine paediatric vaccines in England are co-administered, as recommended in the immunisation schedule as well as never recommended, and assessed potential factors for recommended and never recommended vaccine co-administrations.

### Methods

The data and study population were described in detail before [15]. In brief, data was extracted from the Oxford Royal College of General Practitioners (RCPG) Research and Surveillance Centre (RSC), a national, electronic, primary health care, medical record database, representative for the English population [16,17]. A previous database characterisation study assessed this database and found it fit to provide reliable evidence on vaccination [18]. Calculated vaccine uptake in the RCGP RSC network is similar to national rates published by Public Health England (PHE) [17] while providing access to more granular data than provided by the NHS Cover of Vaccination Evaluated Rapidly (COVER) statistics. We included all children between 0 and 18 years old during the study period from 1 January 2008 to 31 December 2018. Children were excluded from analyses if they were registered in the database after the age for the first scheduled dose of a vaccine. Every child had a unique, anonymised patient identifier. For each child, we also collected the gender, the NHS-region of residence in England, and the postcode-based Index of Multiple Deprivation (IMD) quintiles. Vaccination types, doses, and dates were collected for all routinely scheduled paediatric vaccines by Public Health England between 2008 and 2018: DTaP/IPV/Hib/HepB, DTaP/IPV/Hib, DTaP/IPV, dTaP/IPV, Td/IPV, MMR, PCV, MenB, MenC, MenACWY, Hib/MenC, RV, HPV [9,19–26]. Except for HPV, all these vaccines were scheduled for co-administration. Dose numbers were determined according to the chronological order of vaccinations. Records with a missing patient-ID, vaccination type or date were excluded.

We defined co-administration as having received more than one of the included routine paediatric vaccines on the same day. We distinguished three main categories of co-administration:

1. “Recommended co-administration” for vaccines that were co-administered exactly as recommended in the immunisation schedule;
2. “Deviated co-administration” encompasses vaccine co-administrations that deviate from the actual immunisations schedule. This includes vaccines that are co-administered according to an outdated schedule (“outdated”), vaccines that are co-administered according to the immunisation schedule but not the recommended doses of these vaccines (“shifted doses”), vaccines co-administered according to an outdated schedule and with shifted doses (“outdated and shifted doses”), or co-administrations that lacked at least one of the vaccines scheduled to be co-administered together (“fewer vaccines”).
3. “Never recommended co-administration” for co-administered vaccines that had never been scheduled to be given together.

For each routine paediatric vaccine, the proportion of vaccines co-administered, as well as the amount of vaccines co-administered according to each of the defined categories (i.e. recommended, deviated, never recommended) were calculated. We also identified the ten mostly co-administered vaccines in each of these three categories of co-administration.

We analysed whether recommended, deviated, and never recommended vaccine co-administration differed between the factors gender, NHS region, and IMD quintile, as well as the impact of the timeliness of vaccination, using Pearson’s chi-square test and multivariate logistic regression. We used a significance level of 0.05 to determine whether the co-administration category was independent of any of the potential factors or not. Logistic regression coefficients were transformed to odd ratios to quantify the impact of these factors. Analyses were performed in R [27].

### Results

6,257,828 vaccines in 1,005,827 children met our inclusion criteria for analysis. This study population was representative for the entire population in the database [15]. 1,344,659 (21%) routine paediatric vaccines were given separately, while 4,913,169 (79%) were co-administered: 2,277,482 (36%) vaccines were given with a second vaccine; 2,088,153 (33%) were co-administrations of three, and 541,276 (9%) were co-administrations of four vaccines. Of all 5,782,118 vaccines scheduled for co-administration with at
least one other vaccine, 3’689,268 (64%) were co-administered as recommended in the schedule, 1’039,698 (18%) deviated from the schedule and 181,097 (3%) were co-administered as never recommended, while 872,055 (15%) vaccines were administered separately. As shown in Fig. 2, between 84% and 98% of vaccines scheduled in the first year of age were co-administered with at least one other vaccine, except for Hib/MenC (70%) and the ratio of vaccines co-administered decreased for vaccines scheduled later in life (DtaP/IPV or dTal/IPV, Td/IPV, MenACWY, MMR dose 2). Fig. 2 shows the observed patterns of co-administration for each vaccine and dose: the proportions of each vaccine and dose that were co-administered with other vaccines according to the schedule varied between 87% for DTap/IPV/Hib dose 2 and 17% for both Td/IPV and MenACWY.

We found statistically significant differences for the ratio of vaccines co-administered between genders, NHS regions, and IMD quintiles (p < 0.05). Boys received a larger proportion (85%) of their vaccines co-administered than girls (72% including HPV vaccine, 84% excluding HPV vaccine). Co-administration ratios were higher in London, Midlands and East-England (both 80%) while lower in South England (77%) and North England (78%). There was a slight decrease in the proportion of vaccine co-administrations with decreasing area deprivation from 80% in the first to 78% in the fifth quintile.

The most often co-administered vaccines recommended in the immunisation schedule were DtaP/IPV/Hib + PCV (13.9%), the most often co-administered vaccines that deviated from the schedule were Hib/MenC + MMR + PCV (2.6%), and the most often never recommended co-administered vaccines MMR + Td/IPV (0.6%). The ten most often co-administered vaccines recommended, deviated, and never recommended in the immunisation schedule are listed in Table 1.

Seventy-five percent of co-administrations happened as recommended in the immunisation schedule. Four percent were never recommended. The remaining 21% deviated from the schedule: 10% percent were co-administered according to an outdated schedule ("outdated"), 7% received fewer vaccines than scheduled, 3% had shifted doses, and 1% of co-administered vaccines concerned an outdated co-administration with shifted doses ("outdated and shifted doses"). Fifty-two percent of children received all their co-administered vaccines as recommended in the immunisation schedule, while 19% of children received none of their co-administered vaccines exactly as listed in the schedule. We found statistically significant associations between receiving co-administrations as recommended in the schedule and the factors gender, NHS regions, and IMD quintiles, as well as the timeliness of vaccinations (p < 0.05).

Boys had slightly more co-administrations as recommended (76%) than girls (75%). The proportion of recommended vaccine co-administrations was the highest in North England (78%), 76% in Midlands and East, and South England, while the lowest in London (71%). The ratio of recommended co-administrations was the lowest for areas in the second most deprived quintile (73%) and improved to 78% for areas in the least deprived quintile. We observed 75% recommended co-administrations in the most deprived quintile and 76% in the third and fourth quintiles. The OR for recommended vaccine co-administrations when having received all vaccines on time was 2.46 (95% CI: 2.44–2.48).

Girls were slightly more likely to have never recommended co-administrations (4%) than boys (3%). The highest proportions of deviated and never recommended co-administrations were observed in London (24% and 5%) and the lowest in North England (19% and 3%). The ratios of deviated and never recommended co-administrations were 20% and 4% in Midlands and East England.
and 21% and 3% in South England. Both ratios of deviated and never recommended co-administrations slightly increased with increasing area deprivation (from 20% to 21% for deviated and from 3% to 4% for never recommended co-administrations). Having received at least one vaccine too late increased the odds for deviated co-administrations (OR 1.60; 95% CI 1.58–1.62) and strongly increased the odds for never recommended co-administrations (OR 5.34; 95% CI 5.19–5.50).

Discussion

Our analysis of real-life GP practice data showed that 15% of routine paediatric vaccines scheduled for co-administration in England were administered separately and that more than one third of the vaccines scheduled for co-administration were not co-administered as recommended in the actual immunisation schedule. Almost half of the English children received at least one of their vaccine co-administrations not as recommended in the immunisation schedule, with almost one in five children receiving none of their co-administered vaccines as listed in the schedule. Overall, three quarters of co-administrations happened completely as recommended in the immunisation schedule, while about one fifth of co-administrations deviated from the actual schedule: either different doses or fewer vaccines were given, or co-administration happened according to an outdated schedule. A small proportion of co-administered paediatric vaccines (4%) was not given in line with any immunisation schedule in England during the study period.

The extent to which vaccines were co-administered as recommended in the schedule varied greatly between vaccines. Particularly vaccines scheduled for co-administration after the first year of life were less co-administered according to the schedule, with DTaP/IPV or dTaP/IPV and MMR dose 2 having more than one third never recommended co-administrations or separate administrations. We found that more than 75% of MenACWY and Td/IPV vaccines administered at GP practices were given separately or co-administered as never has been recommended. However, these findings may not be representative for the entire population because these vaccines are typically offered in schools [28] while our study relied on GP data only.

To the best of our knowledge, this is the first study describing vaccine co-administration practices to this extent. We retrieved one study from the United States of America reporting that 65% of eligible children received MenC with Tdap co-administered, and 26% of boys and 28% of girls received Tdap with HPV together. [3] Since these vaccines were not scheduled for co-administration in England these numbers do not allow for a direct comparison. Nevertheless, this study also indicates suboptimal co-administration practices. Despite differences between immunisation schedules in different countries, most vaccines included in our study are part of immunisation programmes in a majority of countries globally [29] and the vaccine co-administrations recommended by the NHS are recommended in multiple other countries too [30,31]. Hence, our findings can be relevant for countries with similar immunisation policies.

Timely vaccination was the major factor for recommended co-administrations. Having received at least one vaccine too late significantly decreased the odds for a recommended vaccine co-administration. We previously found that only about three quarters of eligible children received MenC with MMR, and almost one fifth of children received MenACWY and Tdap co-administered, and 26% of boys and 28% of girls received Tdap with HPV together. [3] Since these vaccines were not scheduled for co-administration in England these numbers do not allow for a direct comparison. Nevertheless, this study also indicates suboptimal co-administration practices. Despite differences between immunisation schedules in different countries, most vaccines included in our study are part of immunisation programmes in a majority of countries globally [29] and the vaccine co-administrations recommended by the NHS are recommended in multiple other countries too [30,31]. Hence, our findings can be relevant for countries with similar immunisation policies.

Although differences between genders, NHS regions, and IMD quintiles were statistically significant, these differences were generally small. This is in line with our previous study that did not find major differences in vaccination timeliness for these factors. [15] Also other studies found that attitudes towards co-administration were barely influenced by socioeconomic determinants [32–34]. On the other hand, parents prefer fewer vaccines co-administered to avoid adverse events and discomfort [32–34] and co-administrations may provoke fear for an increased risk of adverse reactions and undesired effects among health care staff [35]. This indicates that efforts promoting co-administration should address safety concerns among both parents and health care professionals across regions and communities, independent of deprivation.

Co-administrations categorised as deviated in our study merely indicate that immunisations do not happen as recommended. Co-
administering fewer vaccines or other doses than recommended or co-administering according to an outdated schedule may have a limited impact on the health outcomes of the immunisations. However, never recommended co-administrations may lead to undesired and unknown immunogenicity and safety outcomes of the vaccines co-administered, particularly when co-administration occurs off-label [12,13]. Immunisation schedules, including forseen vaccine co-administrations, are designed based on known immunogenicity and safety information as listed on vaccine labels, relying on data from clinical trials including specific vaccine co-administrations. Such evidence may not be available for never recommended vaccine co-administrations. Co-administered vaccines may face inter-vaccine interference which can be caused by competition between vaccines, systemic effects provided by one vaccine affecting the performance of another vaccine, and usage related factors such as the age and dosing interval [13]. These interferences may result in a decreased immune response to one or more of the administered strains [13]. Given the complexity of interactions among co-administered vaccines, gathering and analysing vaccine co-administration data is essential to ensure their ongoing effectiveness and safety in immunisation programmes [5]. Since never recommended vaccine co-administrations are rare, real-world evidence on their effectiveness and safety remains scarce and therefore should be avoided.

In addition, suboptimal co-administration rates negatively affect other benefits associated with co-administration, such as vaccination coverage [2,5,6], vaccine acceptance [5], and lower handling costs [5]. Particularly now that coverage for all paediatric vaccines declines in England, with most coverage rates dropping below the targeted 95% [36], strategies promoting co-administration may help raising vaccine coverage.

Including over 6 million vaccinations in children, obtained from real-life data, our study provides a detailed description of vaccine co-administration practices in England. However, data from medical records may be prone to misclassification and heterogeneous as they are recorded by different persons and institutions to document actual medical practice and not for the purpose of this study. Another disadvantage of relying on existing medical records is that analyses are restricted to the available variables captured in the database. [37] Therefore, we could only explore the potential factors as listed above and must rely on other study designs to further investigate factors of deviated or never recommended co-administration in the future. Our data may also be biased for missingseness, because the RCGP RCS database only collects data from GP practices. However, this effect may be small, as routine childhood vaccines in England are typically given by GPs. [38]

Suboptimal co-administration rates for routine paediatric vaccines indicate that the potential benefits of co-administration are not fully exploited so far. This is a missed opportunity. Further research is needed to quantify the impact on health outcomes and inefficient use of health care resources due to deviated vaccine co-administrations. This would inform concerted public health action to advise parents’ and health care providers’ about the benefits of vaccine co-administration and adequately address potential safety concerns.

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.

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