# Real-life paediatric immunisation practices and the safety of vaccine co-administrations in children

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# Abbreviations

**Vaccines:**

| | |
|---|---|
| DT | Diphtheria and tetanus toxoids vaccine |
| DTaP | Diphtheria and tetanus toxoids and acellular pertussis vaccine |
| DTaP/IPV | Diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine |
| DTaP/IPV or dTaP/IPV | Diphtheria and tetanus toxoids and acellular pertussis adsorbed, and inactivated poliovirus vaccine |
| DTaP/IPV/Hib | Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and Haemophilus influenzae type b conjugate vaccine |
| DTaP/IPV/Hib/HepB | Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, Haemophilus influenzae type b conjugate, and hepatitis B vaccine |
| HepA | Hepatitis A vaccine |
| HepA/HepB | Hepatitis A inactivated and hepatitis B vaccine |
| HepB | Hepatitis B vaccine |
| HepB/Hib | Hepatitis B and Haemophilus influenzae type b conjugate vaccine |
| Hib | Haemophilus influenzae type b conjugate vaccine |
| Hib/Men | Haemophilus influenzae type b conjugate, and bivalent meningococcal conjugate vaccine |
| HPV | Human papillomavirus vaccine |
| IIV (H1N1) | Inactivated influenza vaccine |
| IPV | Inactivated poliovirus vaccine |
| JE | Japanese encephalitis vaccine |
| LAIV | Live attenuated influenza vaccine |
| LJEV | Live attenuated Japanese encephalitis vaccine |
| MenACWY | Quadrivalent meningococcal conjugate vaccine |
| MenB | Serogroup B meningococcal vaccine |
| MenC | Serogroup C meningococcal vaccine |
| MMR | Measles, mumps, and rubella vaccine |
| MMRV | Measles, mumps, rubella, and varicella vaccine |
| MR | Measles rubella vaccine |

| | |
|---|---|
| OPV | Oral polio vaccine |
| PCV | Pneumococcal conjugate vaccine |
| RV | Rotavirus vaccine |
| Td | Tetanus and diphtheria toxoids vaccine |
| Td/IPV | Tetanus and diphtheria toxoids and inactivated poliovirus vaccine |
| Tdap | Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine |
| VAR | Varicella vaccine |
| YF | Yellow fever vaccine |

**Terms:**

| | |
|---|---|
| AEFI | Adverse Events Following Immunisation |
| CIOMS | Council for International Organizations of Medical Sciences |
| COVER | Cover of Vaccination Evaluated Rapidly |
| EKNZ | Ethikkommission Nordwest- und Zentralschweiz |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| GDPR | General Data Protection Regulation |
| GP | General Practitioner |
| GPP | Guidelines for good Pharmacoepidemiology Practices |
| GVP | Good Pharmacovigilance Practices |
| IMD | Index of Multiple Deprivation |
| IQR | Interquartile Range |
| ISPE | International Society for Pharmacoepidemiology |
| NHS | National Health Services |
| OR | Odds Ratio |
| PHE | Public Health England |
| RCGP | Royal College of General Practitioners |
| RECORD | Reporting of Studies Conducted using Observational Routinely-collected Health Data |
| RI | Relative Incidence |
| RIR | Relative Incidence Ratio |
| RSC | Research and Surveillance Centre |

| | |
|---|---|
| SCCS | Self-Controlled Case Series |
| SPC | Summary of Product Characteristics |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| WHO | World Health Organisation |

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The road towards this thesis was slightly longer than anticipated. We have allowed some "detours" along the journey when other projects came up requiring urgent attention. I am glad that we showed flexibility and took up these projects, as these efforts broadened my research experiences that will doubtlessly prove useful in the future.

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# Summary

*Introduction:* Paediatric immunisation schedules are designed to protect children against vaccine-preventable diseases early in life. Thereby, vaccines are often scheduled for co-administration to facilitate the delivery of a growing number of vaccines. However, it may not always be possible for children to adhere to the immunisation schedule. Thus, vaccinations may be delayed, given too early, or missed. Shifted vaccinations may lead to vaccine co-administrations that aren't listed in the schedule. Currently, available information about the safety of real-life vaccine co-administrations versus separate vaccinations is limited and inconclusive. This uncertainty about the safety of co-administered vaccines may nourish vaccine hesitancy and consequently negatively affect immunisation rates. We analysed real-life paediatric immunisation patterns and assessed the relative safety of routine paediatric vaccine co-administration to fill the existing knowledge gap.

*Methods:* Our retrospective, dynamic, population-based cohort study included 1'005'827 children between 0 and 18 years, registered with a General Practitioner in England, participating in the Oxford Royal College of General Practitioners' Research and Surveillance Centre database, between 1 January 2008 and 31 December 2018. We studied 6'257'828 routine childhood vaccinations as recommended in Public Health England's paediatric immunisation schedules during the study period: DTaP/IPV/Hib/HepB, DTaP/IPV/Hib, DTaP/IPV, dTaP/IPV, Td/IPV, MMR, PCV, MenB, MenC, MenACWY, Hib/MenC, RV, HPV. We analysed the timeliness of these vaccinations, characterised co-administration practices, and compared the differences in relative incidences of adverse events following immunisation between separate vaccination and real-life vaccine co-administration using the self-controlled case series method.

*Results:* Seventy-five percent of first vaccine doses were administered on time, 19% too late and 6% too early. Fifty-one percent of second and 45% of third doses of a series were given timely after the preceding dose, 36% of second and 37% of third doses sooner, and 13% of second and 18% of third doses after a longer time. Socio-economic deprivation was associated with poorer schedule adherence for most vaccines and doses.

Seventy-nine percent of all routine paediatric vaccines were co-administered: two vaccines were co-administered in 36%, three in 33%, and four in 9% of co-administrations. Seventy-five percent of vaccine co-administrations were given as recommended in the immunisation schedule, while 4% were never recommended and 21% deviated from the actual schedule (i.e. shifted doses, fewer vaccines, or according to an outdated schedule). Untimely vaccinations were the major determinant for never recommended co-administrations.

Seventeen percent of adverse events following immunisation occurred less and 11% more after co-administrations. Five co-administrations of three vaccines led to amplifying interaction effects. After DTaP/IPV/Hib + MenC + PCV there was an increase in fever, rash, gastrointestinal, and respiratory events. After DTaP/IPV/Hib + MenC + RV there was an increase in gastrointestinal events, and after DTaP/IPV/Hib + PCV + RV there was an increase in fever and respiratory events. After MMR + Hib/MenC + PCV there was an increase in gastrointestinal and respiratory events. After MMR + MenC + PCV there was an increase in gastrointestinal events and general symptoms. Among co-administrations of two vaccines, MMR + PCV led to more fever, rash, and neurological events, MMR + MenC to more fever, and DTaP/IPV/Hib + MMR to more musculoskeletal events compared to separate vaccinations.

*Discussion:* The timeliness of routine paediatric vaccinations was suboptimal and decreased for subsequent doses, particularly after the first year of life. Similarly, the proportions of vaccines co-administered as well as the proportions of recommended co-administrations decreased later in life. Assessing the timeliness of vaccinations in addition to coverage rates is likely to optimise protection and decrease co-administrations without recommendation. Families in lower socio-economic status might particularly benefit from adequate monitoring. We detected no interaction effects following vaccine co-administration for most of the adverse events following immunisation. Routine paediatric vaccine co-administrations that were never recommended weren’t less safe than recommended co-administrations according to our analyses of relative incidence ratios. Co-administering two vaccines led to inhibitory interaction effects for more than a quarter of the studied adverse events. Some amplifying interaction effects after co-administering two vaccines were found for adverse events that occurred less after vaccinations than in the control periods, thus making these events less rare after co-administration than after separate vaccinations. Overall, half of the analysed vaccine

co-administrations had an increased relative incidence for at least one adverse event, particularly after co-administrations of three vaccines. These previously undetected interaction effects indicate a safety signal for such co-administrations. Adding a fourth vaccine wasn't associated with further interaction effects for any of the adverse events following immunisation studied.

*Conclusions:* Children are at risk of suboptimal protection against vaccine-preventable disease during specified periods in their childhood due to untimely vaccinations. Poor immunisation schedule adherence also negatively affects vaccine co-administration practices, forgoing the benefits of co-administering vaccines. We found that real-life co-administrations of two vaccines are at least equally safe as giving the same vaccines separately, while adding a third vaccine may increase the relative incidence of adverse events following immunisation. Building on these findings, we propose enhanced surveillance for a continued and comprehensive evaluation of the burden of adverse events following vaccine co-administrations.

# Zusammenfassung

*Einleitung:* Impfpläne für Kinder sollen früh im Leben vor impfpräventablen Krankheiten schützen. Dabei werden Impfstoffe oft gleichzeitig verabreicht, um die steigende Anzahl von Impfungen in möglichst wenigen Besuchen anzubieten. Der Impfplan bei Kindern kann jedoch nicht immer eingehalten werden. So werden Impfungen verspätet oder zu früh gegeben, oder verpasst. Zeitlich verschobene Impfungen führen dazu, dass Impfstoffe in Kombinationen gegeben werden, die so nicht im Impfplan empfohlen sind. Die derzeit verfügbaren Informationen über die Sicherheit der gleichzeitigen Verabreichung von Impfungen in der Bevölkerung im Vergleich zu separaten Impfungen sind begrenzt und widersprüchlich. Diese Ungewissheit über die Sicherheit von gleichzeitig verabreichten Impfungen kann zu Impfskepsis führen und sich folglich negativ auf die Immunisierungsraten auswirken. Wir haben die Muster der Verabreichung von pädiatrischen Routineimpfungen in der Bevölkerung analysiert und die Sicherheit der gleichzeitigen Verabreichung beurteilt, um die Wissenslücke zu schliessen.

*Methoden:* Unsere retrospektive dynamische populationsbasierte Kohortenstudie umfasste 1'005'827 Kinder zwischen 0 und 18 Jahren, die zwischen dem 1. Januar 2008 und dem 31. Dezember 2018 bei einem Hausarzt in England registriert waren und an der Oxford Royal College of General Practitioners' Research and Surveillance Center Datenbank teilnahmen. Wir haben 6'257'828 Routineimpfungen im Kindesalter studiert, die in den pädiatrischen Impfplänen von Public Health England während des Studienzeitraums empfohlen werden: DTaP/ IPV/Hib/HepB, DTaP/IPV/Hib, DTaP/IPV, dTaP/IPV, Td/IPV, MMR, PCV, MenB, MenC, MenACWY, Hib/MenC, RV, HPV. Wir haben der Planmässigkeit der Impfungen analysiert, Koadministrationspraktiken charakterisiert, und den Unterschieden in der relativen Inzidenz von unerwünschten Ereignissen nach Impfung zwischen einzelnen Impfungen und Koadministrationen verglichen. Letzteres haben wir mit der selbstkontrollierten Fallserien-Methode berechnet.

*Ergebnisse:* Fünfundsiebzig Prozent der ersten Impfdosen wurden rechtzeitig verabreicht, 19% zu spät und 6% zu früh. Einundfünfzig Prozent der zweiten und 45% der dritten Dosis wurden rechtzeitig nach der vorhergehenden Dosis verabreicht. Sechsunddreissig Prozent der zweiten und 37% der

dritten Dosis früher und 13% der zweiten und 18% der dritten Dosis nach längerer Zeit. Sozioökonomische Benachteiligung war für die meisten Impfstoffe und Dosen mit schlechterem Einhaltung des Impfplans verbunden.

Neunundsiebzig Prozent aller pädiatrischen Routineimpfstoffe wurden gleichzeitig verabreicht: In 36% der Koadministrationen wurden zwei Impfstoffe verabreicht, in 33 % drei Impfungen und in 9% vier Impfungen. Fünfundsiebzig Prozent der gleichzeitigen Verabreichungen von Impfungen wurden genau wie im Impfplan aufgeführt verabreicht. Für 4% bestand zu keiner Zeit eine Empfehlung zur gleichzeitigen Verabreichung. In 21% wurde vom aktuellen Impfplan abgewichen (d. h. verschobene Dosen, weniger Impfstoffe, oder gemäss veralteten Impfplan). Zeitliche Abweichungen vom Impfplan waren der wichtigste Risikofaktor für Koadministrationen, die keiner Empfehlung entsprachen.

Siebenzehn Prozent der unerwünschten Ereignisse nach Impfung traten weniger oft und 11% traten häufiger auf nach der gleichzeitigen Verabreichung. Fünf gleichzeitige Verabreichungen von drei Impfungen führten zu verstärkenden Wechselwirkungseffekten. Nach DTaP/IPV/Hib + MenC + PCV kam es vermehrt zu Fieber, Hautausschlag, sowie gastrointestinalen und respiratorischen Ereignissen. Nach DTaP/IPV/Hib + MenC + RV kam es vermehrt zu gastrointestinalen Ereignissen. Nach DTaP/IPV/Hib + PCV + RV kam es vermehrt zu Fieber und respiratorischen Ereignissen. Nach MMR + Hib/MenC + PCV kam es vermehrt zu gastrointestinalen und respiratorischen Ereignissen. Nach MMR + MenC + PCV kam es vermehrt zu gastrointestinalen Ereignissen und allgemeinen Symptomen. Bei gleichzeitiger Verabreichung von zwei Impfungen führte MMR + PCV zu mehr Fieber, Hautausschlag, und neurologischen Ereignissen, MMR + MenC zu mehr Fieber, und DTaP/IPV/Hib + MMR zu mehr muskuloskelettalen Ereignissen im Vergleich zu separaten Impfungen.

*Diskussion:* Die planmässige Verabreichung der pädiatrischen Routineimpfungen war suboptimal und war bei Folgedosen schlechter; besonders nach dem ersten Lebensjahr. In ähnlicher Weise nahmen der Anteil der gleichzeitig verabreichten Impfstoffe sowie die Anteile der empfohlenen gleichzeitig verabreichten Impfstoffe später im Leben ab. Die Analyse der Planmässigkeit von Impfungen, zusätzlich zu den altersspezifischen Durchimpfungsraten kann den Schutz optimieren und das Verabreichen von niecht empfohlenen Koadministrationen verringern. Familien mit niedrigerem sozioökonomischem Status könnten besonders von einer angemessenen Überwachung profitieren. Bei den meisten unerwünschten Ereignissen nach der Immunisierung stellten wir nach gleichzeitiger

Verabreichung des Impfstoffs keine Wechselwirkungen fest. Routinemässige gleichzeitige Verabreichungen von pädiatrischen Impfstoffen, die nie empfohlen wurden, waren laut unseren Analysen der relativen Inzidenzverhältnisse nicht weniger sicher als empfohlene gleichzeitige Verabreichungen. Die gleichzeitige Verabreichung von zwei Impfstoffen führte bei mehr als einem Viertel der untersuchten unerwünschten Ereignisse zu hemmenden Wechselwirkungen. Einige verstärkende Wechselwirkungseffekte nach gleichzeitiger Verabreichung von zwei Impfstoffen wurden für unerwünschte Ereignisse gefunden, die nach Impfungen seltener auftraten als in den Kontrollperioden, wodurch diese Ereignisse nach gleichzeitiger Verabreichung weniger selten auftraten als nach separaten Impfungen. Insgesamt hatte die Hälfte der analysierten gleichzeitigen Verabreichungen von Impfstoffen eine erhöhte relative Inzidenz für mindestens ein unerwünschtes Ereignis, besonders bei gleichzeitigem Verabreichen von drei Impfstoffen. Diese zuvor unentdeckten Wechselwirkungseffekte weisen auf ein Sicherheitssignal für solche gleichzeitigen Verabreichungen hin. Das Hinzufügen eines vierten Impfstoffs hat nicht zu zusätzlichen Wechselwirkungseffekten geführt.

*Schlussfolgerungen:* Kinder sind während bestimmter Zeiträume in ihrer Kindheit aufgrund ausserplanmässiger Impfungen dem Risiko eines suboptimalen Schutzes gegen impfpräventable Krankheiten ausgesetzt. Eine suboptimale Einhaltung des Impfplans wirkt sich auch negativ auf die gleichzeitige Verabreichung von Impfungen aus, wodurch der Gesamtvorteil der gleichzeitigen Verabreichung von Impfungen vermindert wird. Die gleichzeitige Verabreichung von zwei Impfungen in der Bevölkerung erscheint mindestens genauso sicher wie die einzelne Verabreichung derselben Impfstoffe. Bei drei gleichzeitigen Impfungen nimmt die relative Inzidenz von Nebenwirkungen nach der Immunisierung zu. Aufbauend auf diesen Ergebnissen, empfehlen wir eine kontinuierliche und umfassende Beurteilung der Krankheitslast unerwünschter Ereignisse nach gleichzeitiger Verabreichung von Impfungen.

# 1. Introduction

National paediatric immunisation programmes aim to provide an optimal protection against vaccine-preventable diseases early in life, while minimising the risk of adverse events. [1–3] The level of protection against these diseases in the population is a function of vaccination coverage and adherence to the immunisation schedule. Co-administering vaccines is a necessity to organise schedules that are becoming increasingly crowded with the introduction of new vaccines. [4,5] This thesis describes immunisation schedule adherence and non-adherence as well as vaccine co-administration practices. It explores drivers for adherence and co-administration, and quantifies the safety of recommended and other real-life vaccine co-administrations.

## 1.1. Paediatric immunisation schedules

Paediatric immunisation schedules are set by national competent authorities and their advisory boards. [6,7] They are not internationally harmonised and there is still a disparity in terms of access to vaccines between high and low income countries. [8] Globally, most vaccine doses in national immunisation programmes are scheduled before the age of 18, with many in the first year of life. These include combination vaccines (one product against multiple diseases) and vaccine co-administrations (multiple products given at the same healthcare visit). The World Health Organisation recommends immunisation against 27 diseases for children and adolescents as listed in Table 1, of which 19 are recommended in the first year of life. [9] In Switzerland, children under 18 years are vaccinated against 16 diseases by typically 14 injections, of which eight are offered in the first year of life. [10] The routine paediatric immunisation schedule recommended by Public Health England (PHE) and the National Health Services (NHS) is representative of many paediatric schedules in high income countries and is central to the investigations of this thesis. [4,11] It lists 19 recommended injections administered at 8 visits between birth and 14 years of age to protect against 17 different diseases (see Figure 1). [12,13]

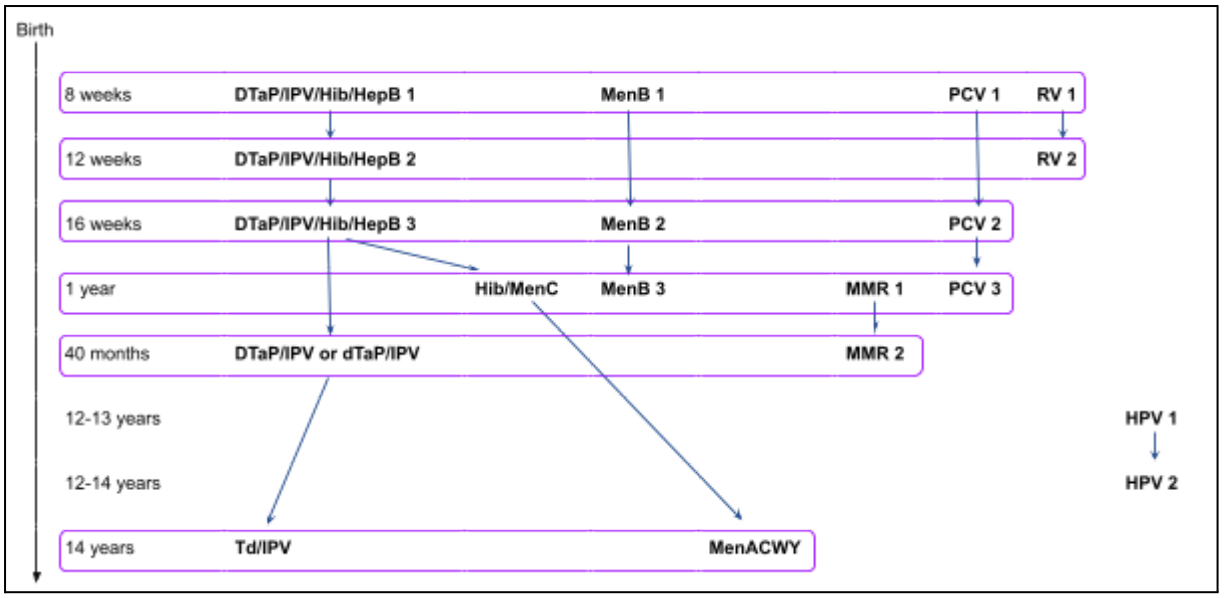


***Figure 1.*** *Vaccine co-administrations as listed in the NHS routine paediatric immunisation schedule 2018. [3,12]*

## 1.2. Immunisation schedule adherence

Strict immunisation schedule adherence in the first years of life may not always be possible for various reasons and vaccinations may be delayed or missed . These reasons include limited access to healthcare, parents' and provider's availabilities, temporary contraindications or preferences (e.g. acute illness of the vaccinee), previous or assumed adverse events following immunisation (AEFI), insufficient information available about a given vaccine, unsatisfactory interactions with healthcare providers, other parents' perceptions, incompatibility with families values or beliefs, distrust in the health system actors and mandatory vaccine policies. [14] Therefore it is important to understand the metrics and drivers of schedule adherence.

Coverage rates are the generally accepted metric of immunisation schedule adherence. Coverage is defined as the proportion of children in an age group who received a vaccine at any time by a defined age. Coverage rates in the English paediatric population which is studied in this thesis, are calculated at 1 year, 2 years, and 5 years of age. [15] They vary between vaccines, ranging from 78% for MMR in 2008-2009 [16] to 95% for DTaP/IPV/Hib in 2012-2013 in England. [17]

However, the timeliness of vaccinations cannot be measured adequately by monitoring coverage because these rates are calculated between eight and 20 months after the recommended ages for the last doses of respective routine paediatric vaccines. [15] Consequently, long periods with lower

coverage may be missed by the conventional monitoring of coverage rates. [13] This impedes the detection of children left vulnerable to vaccine-preventable diseases for longer periods than needed due to delayed doses. For example, between 2001 and 2011 seven children younger than one year died due to pertussis in England, with a disease onset date after the earliest possible protection with a timely vaccination. [18] On the other hand, vaccine doses given too early or at shorter intervals may provoke suboptimal immune responses and confer a false sense of protection. [19–21] Such minimum interval and minimum age violations are the most frequent vaccine administration errors reported. [22] Thus, conventional coverage rates may overestimate the level of protection when vaccines are given untimely. [19] In addition, shifted vaccinations may prompt unscheduled co-administrations of vaccines, e.g. when catching up missed doses, which may cause interference and hence affect both the effectiveness and safety of immunisations [23–25].

Therefore, metrics of timeliness beyond coverage allow a better monitoring of immunisation programmes and informing of public health interventions to improve adherence to immunisation schedules and thus to the health outcomes of immunisations. Nevertheless, most studies addressing adherence to immunisation schedules mainly evaluate coverage to inform immunisation programme implementation. [26] Less is known about the impact of vaccinations deviating from the recommended schedule, such as delayed vaccinations and unscheduled co-administrations.

## 1.3. Vaccine co-administration

Vaccines may be co-administered (i.e. two or more vaccines given at different sites during the same visit), unless contraindicated in the Summary of Product Characteristics (SPC). [27,28] The World Health Organisation's (WHO) does not advise against co-administration and explicitly endorses specific vaccines for co-administration in its position papers for recommended routine immunisations for children, as outlined in Table 1. [29]

***Table 1**. Childhood vaccine co-administrations guidance by the WHO (vaccines underlined are included in the scope of our study). [29]*

| | **Vaccine** | **Eligible population** |
|---|---|---|
| ***Explicitly endorsed***: | BCG | All children |
| | Hepatitis B | All children |
| | Haemophilus influenzae type b | All children |
| | Rubella | All children |
| | Varicella | Children in programmes with certain characteristics |
| ***Not explicitly endorsed:*** | DTP | All children |
| | Rotavirus | All children |
| | Measles | All children |
| | Yellow fever | Children in certain regions |
| | Tick-Borne Encephalitis | Children in certain regions |
| | Typhoid | Children in high-risk populations |
| | Cholera | Children in high-risk populations |
| | Rabies | Children in high risk populations |
| | Mumps | Children in programmes with certain characteristics |
| | Influenza seasonal | Children in programmes with certain characteristics |
| ***Remarks concerning co-administration:*** | | |
| - May be co-administered with other infant vaccines | Polio | All children |
| - Co-administration acceptable | Pneumococcal (conjugate) | All children |

| | | |
|---|---|---|
| - Co-administration with other live and non-live vaccines is possible as separate and simultaneous injections at different injection sites | HPV | All children (girls) |
| - Co-administration of JE and other routine vaccines seems acceptable (despite lack of comprehensive immunogenicity/effectiveness and safety data) | Japanese Encephalitis | Children in certain regions |
| - No evidence for interference when co-administered with other vaccines | Meningococcal (A, C, W, Y) | Children in high-risk populations |
| - Inactivated HepA: can be co-administered simultaneously with other routine childhood vaccines<br>- Live attenuated HepA: No information available on co-administration of live attenuated hepatitis A vaccines with other routinely used vaccines | Hepatitis A | Children in high-risk populations |
| - Co-administration permissible with live and other non-live attenuated vaccines | Dengue | Children in high risk populations |

The 2018 English routine paediatric immunisation schedule – of specific interest to this thesis – recommended six co-administrations, involving 17 injections to protect against 16 diseases, as either two, three, or four injections during a given healthcare practitioner visit (see Figure 1). [3,12] Personal immunisation schemes may lead to more co-administrations because of delays or anticipations necessary for an individual child.

Vaccine co-administration will further gain importance as additional vaccines are integrated to immunisation schedules. New vaccine introductions may lead to more routine doses in an already crowded schedule and to catch-up doses during the introductory phases of new vaccines. Co-administrations can then ease the inclusion of new vaccines into immunisation schedules. Furthermore, scheduling vaccines together can improve immunisation rates for vaccines that are co-administered with other needed vaccines at a given visit, a practice that can applied for example to catch-up delayed vaccinations. [30–32] Co-administration is also a cost-effective immunisation practice as it reduces the number of scheduled healthcare visits. [31,33,34]

However, vaccine co-administration might also negatively affect immunisation rates. When parents decide against the administration of a specific vaccine, the entire appointment may be cancelled and

other vaccines or doses of vaccine series may be missed. [35] If only a specific vaccine was omitted during a given visit, this missing dose may get forgotten at an upcoming routine visit, possibly already filled with other scheduled vaccinations. Parents may also be hesitant to vaccine co-administrations for concerns around overburdening the child's immune system and choose to postpone any of the vaccinations that were scheduled together [36]. This could not only leave children vulnerable during the time of delay period, but it could lead to missed doses and suboptimal protection. Therefore, high quality safety and effectiveness data for vaccine co-administrations is needed for allowing informed public health and clinical decision making.

## 1.4. Safety of vaccine co-administrations

Vaccine co-administrations may cause interference between vaccines and could alter their efficacy and safety profiles, particularly when co-administered off-label. [24,25,33] Both suppressive effects on antibody responses and enhancement effects on cell-mediated immune responses have been observed. [25] Co-administering live-attenuated vaccines sharing similar replicative tissues may cause viral competition, resulting in an impeded immune response to at least one of the administered strains. [25] An epitopic modulating effect can enhance or suppress the immune response and may occur when protein carriers in co-administered vaccines share common epitopes. Inter-product interference may occur due to systemic effects. [25] Eventually, systemic non-specific immune-stimulating or -suppressing effects due to inter-product interference between co-administered vaccines can affect the vaccines' intended immune responses. [25]

The safety outcomes of vaccine co-administrations are typically assessed in pre-licensure clinical trials with children in narrow age ranges, used to inform programme introduction and the design of immunisation schedules. [37] However, a large number of vaccine co-administrations are possible in real practice and are barely evaluated. The numbers and types of vaccines that are co-administered, as well as the vaccinated populations and the age at vaccination in daily practice may differ from those studied in clinical trials. [37] Nevertheless, real-life post-licensure evidence on the extent and impact of vaccine co-administrations on immunogenicity and safety profiles is scarce. [37]

Most studies specifically assessing the safety differences between co-administered vaccines and separately administered vaccines are designed to primarily demonstrate efficacy rather than thoroughly evaluating AEFI. [37] Only 50 from 185 reviewed studies assessing the safety of vaccine

co-administrations between 1999 and 2019 directly compared co-administration with separate administration of the same vaccines, focussing on European countries and the USA. [37] Most of these fifty studies were randomised clinical trials (RCTs) focussing on efficacy and only briefly addressing safety. Given the low incidence of adverse events following immunisation (AEFI), the sample sizes in such trials may be insufficient to detect statistically significant safety differences. [37,38] Two thirds of these studies reported safety differences that were not statistically significant, while one third of studies shared only absolute numbers or percentages without any information about the statistical significance of the safety outcomes. [37] Direct comparisons between separate vaccinations and co-administration were not possible in the other studies because control groups in these studies received the antigens in a combined vaccine, fewer or other antigens, or no vaccines. [37]

Some studies found differences in the incidence of common, less severe AEFIs between co-administered vaccines and the same vaccines administered separately. [37] However, either these vaccine co-administrations were evaluated in only one study each, or the findings were not confirmed by the few other studies on the same vaccines. [37] This lack of repeated studies together with poor statistical power in many of the available studies, leads to an absence of confirmatory results in the presence or contradictory findings. [37] In addition, vaccine co-administration studies with inadequate immunogenicity and/or undesired safety outcomes may not be published. [37] Such a publication bias favouring studies with a positive benefit–risk balance urges us to appraise the available evidence critically.

Overall, the available evidence is limited and provides inconclusive information about the safety of paediatric vaccine co-administrations compared to separate vaccinations. [37] This constricts the potential for a thorough assessment of the safety of vaccine co-administrations and for well informed clinical decision making.

## 1.5. Relevance for public health

Public health policies and immunisation schedules might not always be in line with a vaccine’s label. [39] For example, vaccination might be scheduled at different ages or another dose regimen than specified in the label. [39] Furthermore, a large number of potential vaccine co-administrations that are neither specified in the label, nor listed in immunisation schedules are possible and occur in practice.

Nevertheless, not much is known about off-label use of vaccines in the paediatric population. Real-life data about the use, efficiency, and safety of vaccines – including co-administration practices – can provide evidence to update vaccine labels, regulatory decision making, and to inform public health organisations on vaccination programme recommendations and immunisation schedules.

Vaccine hesitancy can be nourished by uncertainty about the safety of vaccine co-administration. [40,41] Parents can be concerned about the increasing number of vaccine co-administrations, which is a potential source of an upcoming larger loss of public confidence in vaccination programmes, if solid evidence on the safety of co-administrations is not available ahead of time. A lack of timely safety information or misguided public decision making gives room to speculation and concern and could derail generally safe and effective immunisation programmes. Eventually, opposition to vaccination and under-vaccination may jeopardise individual and herd immunity. [42] Thus, it is of paramount importance that parents' doubts about the health outcomes and particularly the safety of co-administered vaccines are addressed with accurate information, meeting the needs of both healthcare providers and parents [43].

## 1.6. Relevance for clinical practice

The large number of paediatric vaccines and doses as well as changing immunisation schedules can create challenging situations for healthcare practitioners. It can become complex to assess a child's vaccination status, for example whether the child has fallen behind the immunisation schedule or received invalid doses. [44] Administering a wrong vaccine or dose to a child of an inappropriate age (i.e. before the minimum age or interval, or late dosing), two live vaccines given within less than four weeks time, or inappropriate vaccine co-administrations are commonly reported vaccination errors. [22,45] Insight in the causes of such errors is essential for designing appropriate solutions to minimise and avoid these errors in future clinical practice. Information about the clinical implications of such errors, such as the safety of inappropriate vaccine co-administrations addressed in this thesis, is useful to determine the appropriate actions should such errors occur.

## 1.7. Research needs

Dedicated research into the safety of vaccine co-administration is essential to generate the necessary evidence for confident decision making about immunisations at the public health and the individual patient level. Potential risks from preventive measures, such as immunisation, should be as low as possible. [37] Therefore, vaccine co-administration practices must be supported by evidence that co-administrations are effective and equally safe as separately administered vaccines. [46] This can be achieved by studying and monitoring the safety of paediatric immunisation schedules. Specifically, the Institute of Medicine recommends studying whether health outcomes differ for children who receive fewer immunisations per physician visit. [47]

Our initial systematic review of the available literature concerning the safety of paediatric vaccine co-administration revealed that this subject is insufficiently investigated. [37] Our goal was to address this paucity of evidence with the study described in this thesis. First, we described the timeliness of paediatric vaccinations and explored potential factors for adherence and non-adherence. Second, we described paediatric vaccine co-administration practices, assessed whether these occur as recommended in the immunisation schedule, and explored potential factors for never recommended co-administrations. Finally, we evaluated the safety of both recommended and never recommended real-life paediatric vaccine co-administrations.

# 2. Aim and objectives

The aim of this thesis was to describe real-life paediatric immunisation practices and to quantify the safety of routine paediatric vaccine co-administrations. We defined the following primary and secondary objectives to achieve this:

1. To assess the adherence (timeliness) of routine paediatric vaccinations according to Public Health England's paediatric immunisation schedule
    a. To calculate the prevalence of on time, early and delayed vaccinations
    b. To explore potential factors of adherence to the immunisation schedule
2. To quantify the extent of routine paediatric vaccines that are co-administered as recommended as well as never recommended in the immunisation schedule
    a. To calculate the prevalence of any recommended and never recommended vaccine co-administrations
    b. To explore potential factors of never recommended vaccine co-administration
3. To analyse interaction effects for adverse events following immunisation (AEFI) when co-administering routine paediatric vaccines as recommended as well as never recommended in the immunisation schedule
    a. To calculate the relative incidences (RI) of AEFI for vaccines administered separately and co-administered
    b. To calculate the relative incidence ratios of AEFI after the co-administration of vaccines to the AEFI after administering the same vaccines separately.

# 3. Methods

## 3.1. Study design

We designed an observational, retrospective dynamic population-based standard risk interval cohort study. Thereby taking into consideration relevant guidelines for pharmacovigilance studies, including: the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidance for pharmacoepidemiology and pharmacovigilance studies [48], the International Society for Pharmacoepidemiology's (ISPE) guidelines for good pharmacoepidemiology practices (GPP) [49], the Council for International Organizations of Medical Sciences' (CIOMS) report "Definition and application of terms for vaccine pharmacovigilance" [50], and the Good pharmacovigilance practices (GVP) module on vaccines [51].

## 3.2. Population

Our study comprised a dynamic cohort of 1 005 827 children aged 0 to 18 years, registered at a General Practitioner in England between 1 January 2008 and 31 December 2018, providing data to the Oxford Royal College of General Practitioners' (RCGP) Research and Surveillance Centre (RSC) database. Children who entered the database after the scheduled age for the first dose of a specific vaccine, were excluded from analyses concerning that vaccine type.

## 3.3. Database

The database selection and secondary data collection and handling occurred in line with the ISPE-endorsed Guidelines for Good Database Selection and use in Pharmacoepidemiology Research. [49] The completeness of data capture, bias, and the validity of data for exposure and outcomes variables as well as covariates was assessed as recommended by ENCePP. [48] We used the Strengthening the reporting of observational studies in epidemiology (STROBE) [52] and Reporting of studies conducted using observational routinely-collected health data (RECORD) [53] checklists to capture and eventually transparently report all critical information.

We extracted population-based data from the RCGP RSC. This national, electronic primary healthcare medical record database comprises 155 general practices in England, with a population of more than

1.5 million patients. The population is largely representative of the English census. [54,55] It covers a broad distribution of patients across England and prescription rates in line with those reported at the national level by the British National Formulary. [56] Data are extracted twice weekly from practice systems. Children whose parents have withheld consent for data sharing are automatically excluded from analyses through an opt-out code. Data are pseudonymised and held on secure servers at the University of Oxford in England with access by investigators only, compliant with NHS data governance rules. [56] All analyses were conducted on de-identifiable datasets that remained stored on these servers.

Children had a unique, anonymised identifier in the dataset. We collected the month and year of birth), gender, the NHS-region of residence (North England; Midlands and East England; London; South England), and the postcode-based Index of Multiple Deprivation (IMD) quintiles (1 being most deprived, 5 being least deprived) for every child [57]. All routine paediatric vaccination types and doses in series, vaccination dates, adverse event types, and adverse events onset dates during the study period were extracted. The data was cleaned, i.e. variability in the registration of immunisations and events (different coding, different use of names) was homogenised (using standardised naming/coding of vaccines and events). Records with incomplete information (e.g. missing identifier, vaccination type, or vaccination date) or erroneous information were excluded from the analysis.

## 3.4. Scope

For exposure, we included all routine childhood vaccines listed in Public Health England's paediatric immunisation schedules 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. [12,58–65] The safety assessment was done for the 10 most frequent recommended vaccine co-administrations and the 10 most frequent real-life vaccine co-administrations that have never been recommended. [37] The safety outcomes comprised adverse events for which scientific evidence for a causal relation with vaccination is available, selected following an initial systematic literature review of safety studies on vaccine co-administration [37].

## 3.5. Analyses

All analyses followed a statistical analysis plan and were performed using the statistical software R [66]. We have organised our analysis in three parts.

### 3.5.1. Adherence to the paediatric vaccination schedule

For the first doses of a vaccine, we defined timely vaccination as vaccines given at or within one month after the recommended age for vaccines scheduled in the first year of life, or within two months for vaccines scheduled later in life. We defined timely vaccination for subsequent doses as doses given at the recommended interval or within one month thereafter for doses scheduled in the first year of life, or within two months for doses scheduled later in life. The recommended ages and the intervals between subsequent doses correspond with the ages and time between the ages described in the immunisation schedule that was valid at the time of vaccination. The time windows were based on immunisation guidelines, and other studies applying similar windows. [28,67–77] First doses given before the recommended age were categorised as early and those after the time window as late. Subsequent doses given within a shorter period than recommended were classified as having a too short gap, or when given beyond the time window as having a too long gap. Missed vaccinations were not considered.

We calculated the timeliness of vaccination for each vaccine and dose as the proportion of children who received the vaccine within the defined windows, reflecting adherence to the immunisation schedule. The proportions of early and late first doses, and too short and too long gaps between subsequent doses were calculated accordingly. The deviation of vaccinations around the scheduled age was assessed for each vaccine and dose. We evaluated differences in timeliness between genders, IMD quintiles, and NHS regions, as well as the impact of preceding doses' timeliness, using multivariate logistic regression and Pearson's chi-square test. We applied a significance level of 0.05 to determine whether on time vaccination was independent of any of these covariates. The impact of these factors was quantified by converting the logistic regression coefficients into odds-ratios. We performed sensitivity analyses to evaluate the impact of variables that might lead to bias.

Basic logistic regression model:

*glm(OnScheduleYN ~ Gender + as.factor(IMDQuintile) + NHSRegion, family = binomial, df )*

- glm: generalised linear model
- Depending variable (e.g. OnScheduleYN): Dichotomous: vaccine dose on time (1) or not (0), similarly for early, late, too short, and too long gaps
- Covariates: Gender: IMD quintile, NHS region

### 3.5.2. Co-administration of paediatric vaccines

Co-administration was defined as receiving more than one vaccine on the same day, with three categories of co-administration:

1. “Recommended co-administration”: vaccines co-administered exactly as recommended in the immunisation schedule valid at the time of vaccination

2. “Deviated co-administration” comprises:

    - Co-administrations according to an outdated schedule (“outdated”)
    - Co-administrations according to the immunisation schedule but not the recommended doses of these vaccines (“shifted doses”)
    - Co-administrations according to an outdated schedule but with shifted doses (“outdated and shifted doses”)
    - Co-administrations lacking at least one of the vaccines scheduled to be co-administered (“fewer vaccines”)

3. “Never recommended co-administration”: co-administered vaccines that had never been scheduled together.

We calculated the proportions of each vaccine and dose given separately or co-administered, and the proportions of co-administered vaccines according to each of the categories defined above. Differences in recommended, deviated, and never recommended vaccine co-administration between genders, IMD quintiles, and NHS regions, as well as the impact of vaccination timeliness, were evaluated by multivariate logistic regression and Pearson’s chi-square test, with a significance level of 0.05 to determine whether co-administration in each category was independent of any of these

covariates. The impact of these factors was quantified by converting logistic regression coefficients into odds-ratios.

### 3.5.3. Pharmacovigilance: Safety of vaccine co-administrations

Our vaccine safety surveillance study adopted a signal generating approach to detect possible associations between vaccinations and adverse events without a prior hypothesis [78]. We applied parallel group non-randomised cohort analyses to compare the incidences of AEFI in children who received co-administered vaccines with children who received the same vaccines separately. By restricting comparisons to vaccinated individuals we avoid selection bias when comparing adverse event rates in vaccinated and unvaccinated individuals (due to non-randomly allocating vaccines) [78].

We analysed the safety of both recommended and never recommended vaccine co-administrations through a standard risk interval methodology using self-controlled case series (SCCS) [79,80]. Incidences of AEFI in post-vaccination exposure periods were compared to incidences of these events in unexposed periods (encompassing the time that children were registered in the database while between 0 and 18 years of age) within persons, and quantified as relative incidences (RI). [81] Post-vaccination risk intervals correspond to a biologically plausible window after vaccination when AEFI could occur. [82,83] Given the complexity and paucity of information on evidence about immune-interference between co-administered vaccines, we applied a risk interval of 42 days to assure that most AEFI were captured. Such long risk intervals are commonly used in vaccine pharmacovigilance studies, particularly in the early surveillance of vaccine safety [82], and adequate for hypothesis generating studies.

We used a fitted self-controlled case series (SCCS) conditional semiparametric Poisson model programmed with the SCCS package [84] in R to estimate the (RI) of each type of AEFI following both separate and co-administration of the same vaccines. This SCCS model estimates the RI of an AEFI for each vaccine in absence of other vaccines, corresponding to separate administrations (e.g. $RI_{vaccine\ a}$, $RI_{vaccine\ b}$). The model also calculates an interaction term quantifying the effect of co-administration on the individual vaccines' RIs. This term is a relative incidence ratio (RIR), corresponding to the ratio of the RI in the co-administration group compared to the RI in the separate vaccination reference group. [81] Ultimately, multiplying the individual RIs with the interaction term ($RIR_{interaction}$) results in the RI following vaccine co-administration ($RI_{co\text{-}administered}$):

$$RI_{co\text{-}administered} = RI_{vaccine\ a} \times RI_{vaccine\ b} \times RIR_{interaction}$$

An interaction term significantly less than 1 ($p<0.05$) reveals an inhibitory interaction effect as the $RI_{co\text{-}administered}$ is lower than expected based on the RIs for the separately administered vaccines. Correspondingly, an interaction term significantly greater than 1 ($p<0.05$) reveals an amplifying interaction effect.

## 3.6. Ethics

This study was conducted under the principles of the World Medical Association Declaration of Helsinki [85], respecting local and European legislation concerning data protection, including the General Data Protection Regulation (GDPR) [86]. A separate Ethics Committee approval was not required for this study as confirmed by the NHS Health Research Authority and the Ethics Committee for Nord-West and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz (EKNZ)). The use of patient data was justified by the anticipated value of the analyses and outcomes, aiming at protecting the health of future generations through informing and improving future immunisation schedules and practices for children.

# 4. Publications

The following four publications detail the findings of our study:

1. Manuscript 1: Bauwens J, Saenz LH, Reusser A, Künzli N, Bonhoeffer J. **Safety of co-Administration versus separate administration of the same vaccines in children: a systematic literature review.** *Vaccines* 2020;8. https://doi.org/10.3390/vaccines8010012
2. Manuscript 2: Bauwens J, de Lusignan S, Sherlock J, Ferreira F, Künzli N, Bonhoeffer J. **Adherence to the paediatric immunisation schedule in England.** *Vaccine X* 2021;9. https://doi.org/10.1016/j.jvacx.2021.100125
3. Manuscript 3: Bauwens J, de Lusignan S, Sherlock J, Ferreira F, Künzli N, Bonhoeffer J. **Co-administration of routine paediatric vaccines in England often deviates from the immunisation schedule.** *Vaccine X* 2021;9. https://doi.org/10.1016/j.jvacx.2021.100115
4. Manuscript 4: Bauwens J, de Lusignan S, Weldeselassie YG, Künzli N, Bonhoeffer J. **Safety of routine childhood vaccine coadministration versus separate vaccination.** *BMJ Global Health* 2022;7:e008215. https://doi:10.1136/bmjgh-2021-0082152022

# Manuscript 1: **Safety of co-Administration versus separate administration of the same vaccines in children: a systematic literature review**

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vaccines

MDPI

*Review*

# Safety of Co-Administration Versus Separate Administration of the Same Vaccines in Children: A Systematic Literature Review

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**Abstract:** The growing number of available vaccines that can be potentially co-administered makes the assessment of the safety of vaccine co-administration increasingly relevant but complex. We aimed to synthesize the available scientific evidence on the safety of vaccine co-administrations in children by performing a systematic literature review of studies assessing the safety of vaccine co-administrations in children between 1999 and 2019, in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Fifty studies compared co-administered vaccines versus the same vaccines administered separately. The most frequently studied vaccines included quadrivalent meningococcal conjugate (MenACWY) vaccine, diphtheria and tetanus toxoids and acellular pertussis (DTaP) or tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccines, diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B, inactivated poliovirus and *Haemophilus influenzae* type b conjugate (DTaP-HepB-IPV/Hib) vaccine, measles, mumps, and rubella (MMR) vaccine, and pneumococcal conjugate 7-valent (PCV7) or 13-valent (PCV13) vaccines. Of this, 16% (n = 8) of the studies reported significantly more adverse events following immunization (AEFI) while in 10% (n = 5) significantly fewer adverse events were found in the co-administration groups. Statistically significant differences between co-administration and separate administration were found for 16 adverse events, for 11 different vaccine co-administrations. In general, studies briefly described safety and one-third of studies lacked any statistical assessment of AEFI. Overall, the evidence on the safety of vaccine co-administrations compared to separate vaccine administrations is inconclusive and there is a paucity of large post-licensure studies addressing this issue.

**Keywords:** children; minors; vaccination; vaccines; safety; adverse effects; co-administration

## 1. Introduction

With new vaccines becoming available and added to pediatric immunization schedules, these schedules become increasingly crowded [1,2]. Since co-administering vaccines may facilitate the introduction of new vaccines to immunization schedules and positively affect coverage rates [3], a growing number of vaccines is likely to be co-administered in the future. Uncertainty about the safety of co-administered vaccines can contribute to vaccine hesitancy in parents [4,5]. This highlights the need for assessing the safety of co-administered vaccines.

Immunization schedules are typically designed based on evidence of efficacy and safety from clinical trials. However, both the number and types of vaccines co-administered in routine

immunization practices, as well as the vaccinated populations, may differ from the ones investigated in pre-licensure trials. In addition, the small sample size of clinical trials, the many possibilities of vaccine co-administrations, and the low incidence of adverse events following immunization (AEFI) make it challenging to find and interpret evidence on the safety of vaccine co-administrations compared to separate administrations. Both healthcare providers and parents require more information about vaccine co-administrations [6]. Therefore, we performed a systematic literature review, aiming to synthesize the available scientific evidence on the safety of vaccine co-administrations in children.

## 2. Methods

We performed a systematic literature review of studies assessing the safety of vaccine co-administrations in children in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our search strategy aimed to retrieve studies in the pediatric population, who received more than one vaccine at the same time for which adverse outcomes were reported. We searched Pubmed (including Medline), Embase, and the Cochrane library for articles in English, published between 1999 and 2019 to cover vaccines and co-administrations relevant to actual immunization practices, combining the following keywords:

- Population: Infant OR child OR adolescent OR newborn OR minors OR teenager;
- Intervention: Vaccination OR vaccines OR immunization OR immunization schedule OR immunization OR immunization, secondary/trends OR mass vaccination/trends OR vaccines/administration & dosage OR vaccines/pharmacology; and
- Outcome: ((Safety drug-related side effects OR adverse reactions OR adverse effects OR vaccination/adverse effects OR vaccines/complications OR vaccines/adverse effects) OR safety OR tolerability) AND (co-administration OR co-administered OR concomitant administration OR simultaneous administration).

This translated in the following search string for Pubmed: "(Infant OR child OR adolescent OR newborn OR minors [MeSH terms]) AND (vaccination OR vaccines OR immunization OR immunization schedule OR immunization OR immunization, secondary/trends OR mass vaccination/trends OR vaccines/administration and dosage OR vaccines/pharmacology [MeSH terms]) AND ((safety drug-related side effects OR adverse reactions OR adverse effects OR vaccination/adverse effects OR vaccines/complications OR vaccines/adverse effects [MeSH terms]) OR safety) AND (co-administration OR co-administered OR concomitant administration OR simultaneous administration)". The most recent search was performed on 28 January 2019. We screened the included articles' reference lists for additional articles. Full text articles were obtained through the University of Basel's library and references were managed using Zotero [7].

Articles were eligible when study participants were under 18 years of age or the study population included both under and over 18 year olds, co-administration of at least two vaccines was indicated in the title and/or abstract, and safety data were reported. After removing duplicates, the following data was collected from the included articles by three independent reviewers (J.B. (Jorgen Bauwens), L.-H.S., A.R.). Study population: Minimum and maximum age of children included, sample size, selected inclusion and exclusion criteria applied (i.e., subpopulations, conditions leading to exclusion). Intervention: Vaccines co-administered and comparator vaccines. Outcome: All AEFIs observed, reported differences in AEFI between co-administration and comparator groups (i.e., statistically significantly more or fewer AEFI, more or fewer AEFI without statistical assessment). Study characteristics: Study design, countries, statistics reported to assess differences in AEFI, potential sources of bias. Coding, completeness, and consistency of variables in the data extraction forms were checked among the reviewers and data were compiled in a structured database.

The safety assessment was limited to studies comparing co-administered vaccines with the same vaccines administered separately. Studies where the comparator group did not receive exactly the same vaccines separately as the vaccines co-administered were excluded. For studies comparing

co-administration with separate administration of the same vaccines, the collected data was analyzed to obtain the following summary measures: Vaccines investigated in co-administration versus separate administration of the same vaccines and their frequencies of occurrence among the included studies; frequencies of study designs used to assess co-administration versus separate administration; minimum, maximum, and mean sample sizes of the included studies by study design; minimum and maximum ages of children in the included studies; number of studies per country; number of studies with statistically more or statistically fewer AEFI between both groups, number of studies with more or fewer AEFI between both groups without statistical assessment provided; AEFI that were reported statistically significantly more or less between both study groups; use of statistical measures in the included studies; occurrence of potential sources of bias including health status of the study population, exclusion of children with known previous reaction or allergies to vaccines or vaccine components; and method for reporting and collecting AEFIs. Analyses were performed in R [8].

## 3. Results

From 391 retrieved articles, 185 studies reported safety data for co-administration of at least two vaccines in children. Of these, 50 studies (27%) compared co-administration with separate administration of the same vaccines and were included in our analysis. Other studies meeting the initial inclusion criteria, but not allowing a direct comparison between co-administration and separate administration, compared co-administered vaccines versus only a part of the same vaccines administered separately (n = 56, 30%), versus the same antigens but combined in one vaccine (n = 20, 11%), versus other vaccines (n = 6, 3%), or looked at co-administered vaccines without comparison (n = 58, 31%). Figure 1 displays the study attrition diagram.

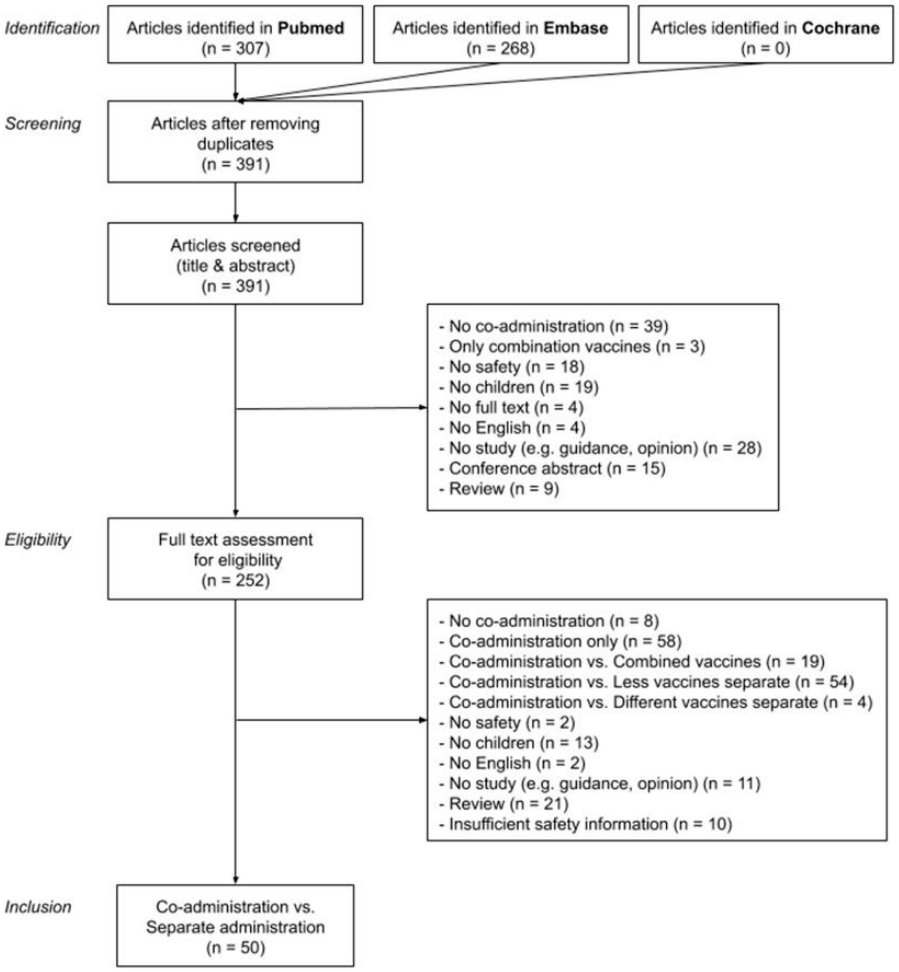


**Figure 1.** Flow diagram of identifying, screening, assessing eligibility, and including studies.

### *3.1. Vaccines Studied*

The most frequently investigated co-administered vaccines included MenACWY vaccine (n = 16, 32%), DTaP or Tdap vaccines (n = 11, 22%), DTaP-HepB-IPV/Hib vaccine (n = 10, 20%), MMR vaccine (n = 9, 18%), and PCV7 or PCV13 vaccines (n = 9, 18%) (Figure 2). Supplementary Table S1 provides an overview of the study characteristics and findings of all studies comparing co-administered vaccines versus the same vaccines administered separately. The full meaning of vaccine abbreviations can be found in Supplementary Table S2.

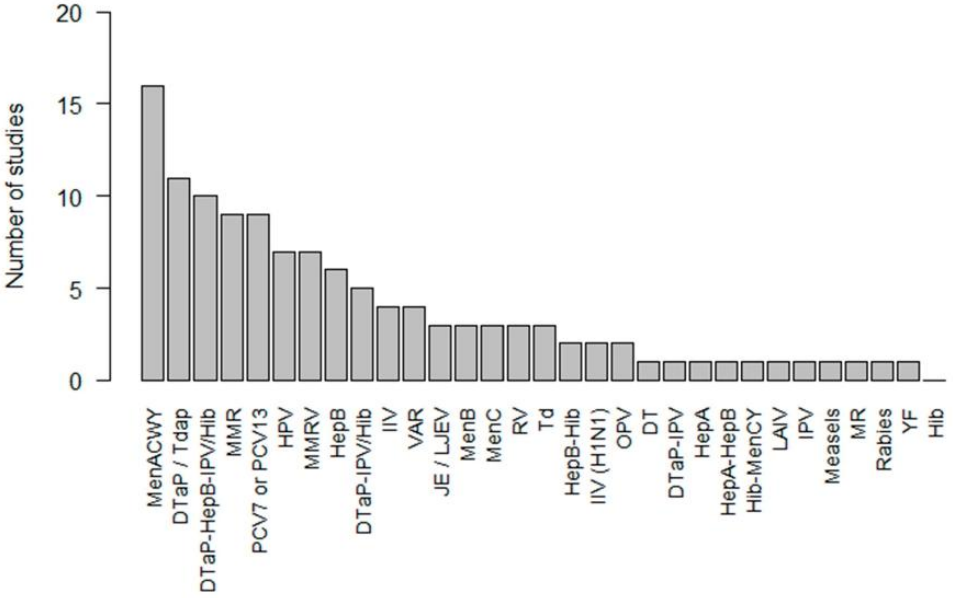


**Figure 2.** Frequency of vaccines investigated in co-administration versus separate administration studies.

*3.2. Study Characteristics*

The median sample size of the 50 studies comparing co-administration with separate administration of the same vaccines was 726 (interquartile range (IQR) 328-1199). Forty-five (90%) of these studies were randomized clinical trials with a sample size between 64 and 2648 children. One case-control study included 590 children. One prospective observational study had a study size of 530 children and one retrospective observational study included 36,844 children. One study used surveillance data covering 128,197 vaccinations and one study used case reports from 883 children. Table 1 lists the sample sizes of these trials by phase. The minimum ages of children enrolled in the studies varied between birth and 16 years (median 1 year) and the maximum ages of the enrolled study population varied between 7 weeks and 49 years (median 23 months). Seven studies (14%) also included persons over 18 years whose data were deemed relevant for assessing the safety of co-administration and were therefore included in our analysis. Figure 3 shows the geographic distribution of these studies and highlights that studies were particularly conducted in the US and Europe.

Only healthy children were enrolled in 37 (74%) studies and 20 studies (40%) excluded children with known allergies or hypersensitivity to vaccines or vaccine components. In 37 (74%) studies, the safety data relied on parental self-reporting of AEFI.

**Table 1.** Sample sizes by study type.

| Study Type | n | Minimum | Sample Size Median | Maximum |
|---|---|---|---|---|
| RCT (no phase specified) | 27 | 64 | 550 | 2503 |
| RCT phase 2 | 3 | 200 | 2499 | 2648 |
| RCT phase 2b | 1 | | 460 | |
| RCT phase 3 | 9 | 312 | 802 | 1620 |
| RCT phase 3b | 2 | 716 | 730 | 744 |
| RCT phase 4 | 3 | 376 | 1341 | 1504 |
| Case Control | 1 | | 590 | |
| Prospective Observational Cohort | 1 | | 530 | |
| Retrospective Observational Cohort | 1 | | 36,844 | |
| Surveillance report | 1 | | 128,297 | |
| Case Reports | 1 | | 833 | |

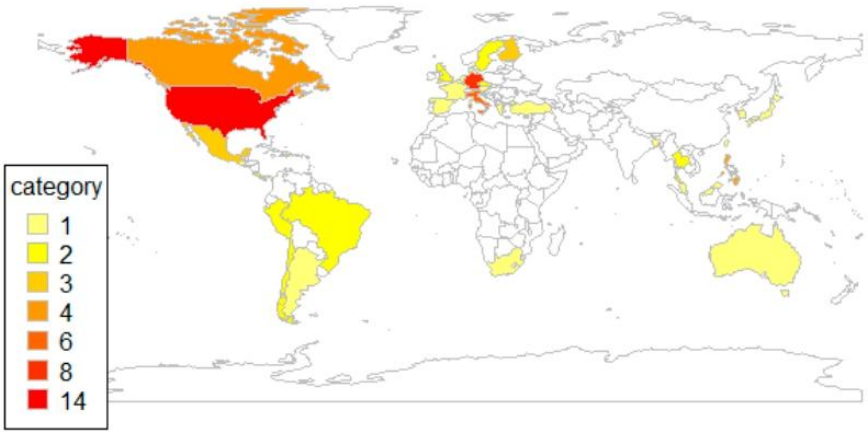


**Figure 3.** Geographical distribution of studies comparing co-administration versus separate administration.

### *3.3. Safety Outcomes*

Thirteen (26%) studies comparing co-administered vaccines with the same vaccines administered separately found statistically significant safety differences. Of these, eight studies (16%) reported significantly more and five studies (10%) reported significantly fewer AEFI in the respective co-administration groups. Of the eight studies identifying significantly more AEFI, two found significant increases in pyrexia: One when co-administering PCV13 + IIV3 (RD: 20.6%, RR: 2.2) and one when co-administering DTaP-HepB-IPV/Hib + PCV7 (RD: 14.7%, RR: 2.5) compared to separate administration of these vaccines [9,10]. One study reported significant increases in injection site pain (risk difference (RD): 6.3%, relative risk (RR): 1.1) and injection site bruising (RD: 3.6%, RR: 2.6) when co-administering MenACWY + Tdap + HPV compared to separate administration [11]. One study reported significant increases in injection site swelling (RD: 5.0%, RR: 1.5) when co-administering MenACWY + Tdap + HPV compared to separate administration [12], and one study reported a significant increase in myalgia (RD: 16%, RR: 1.5) after co-administering MenACWY + Tdap + HPV [13]. One study reported significant increases of injection site tenderness (RD: 15.6%, RR: 2.7) and headache (RD: 22.9%, RR: 3.7) after co-administering Td + MMR + HepB compared to separate administration [14]. One study reported a significant increase in vomiting (RD: 10.0%, RR: 2.0) following DTaP-IPV/Hib + MenC + RV5 co-administration [15], and one study reported significant increases in overall adverse

events following co-administration (RD: 19.1%, RR: 1.5) of DTaP-IPV/Hib + MMR compared to their separate administrations [16].

Of the five studies identifying significantly fewer AEFI, one study reported significantly less diarrhea (RD: −20.3%, RR: 0.5) and pyrexia (RD: −11.3%, RR: 0.5) following co-administration of DTaP-IPV + RV5 [17]. One study reported significantly less injection site erythema (RD: −15.4%, RR: 0.7) following DTaP-HepB-IPV/Hib + MenC co-administration [18]. One study reported significantly less rash (RD: −5.8%, RR: 0.6) and rhinorrhea (RD: −6.1%, RR: 0.7) after + MMR + VAR + Hib-HepB co-administration compared to separate administration [19]. One study reported significantly less nasopharyngitis (RD: −3.5%, RR: 0.6) and insomnia following co-administering PCV7 + MMRV compared to separate administration [20]. One study reported significantly less conjunctivitis (RD: −0.7%, RR: 0.1) after co-administering OPV and LAIV compared to separate administration [21]. The reported incidences of AEFIs are presented in Figure 4. Supplementary Table S1 provides a summary of the major study characteristics.

Thirty-three (66%) of studies comparing co-administered vaccines versus the same vaccines administered separately reported safety differences without providing a statistical assessment: In 29 (58%) of these studies increased AEFI were found in the co-administration groups and in 17 (34%) of these studies decreased AEFI were found in the co-administration groups.

Risk of AEFI and differences between groups were statistically evaluated and reported in studies comparing co-administration with separate administration of the same vaccines by assessing confidence intervals (48%), p-values (28%), risk differences (10%), relative risks (4%), Fisher test (2%), adjusted relative risk (aRR) (2%), IR (1%), or odds ratios (2%). Seventeen (34%) studies reported no statistical assessment. Of those, two studies (4%) listed observed AEFI without reporting absolute numbers or percentages.

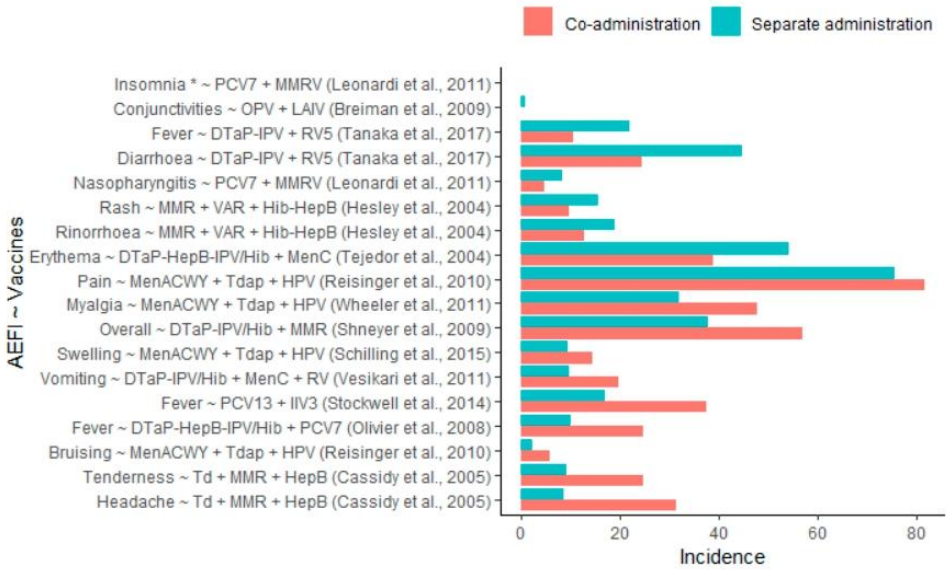


**Figure 4.** Incidences of adverse events following immunization (AEFIs) with statistically significant differences following co-administration compared to separate administration. *No incidences reported.

## 4. Discussion

The evidence about the safety of co-administered vaccines compared to separately administered vaccines is mainly based on clinical trials that were primarily designed to evaluate efficacy rather than safety differences. The safety of co-administering vaccines was assessed in 185 studies over the last 20 years. Of these, only 50 directly compared the safety of co-administration with separate

administration of the same vaccines. Most occurred in Europe and the USA, reflecting the regions where the most clinical trials take place [22] and where databases with observational data are available. The remaining 135 studies assessed the safety of co-administration and revealed safety data but did not allow a comparison with separate administration because they lacked a control group who received the same antigens as separate vaccines. The control groups in these studies received fewer antigens, received the antigens in a combined vaccine, received other antigens, or the control group did not receive any vaccine.

For the majority of co-administered vaccines, only one study directly assessing the safety of vaccine co-administration versus separate administration was available. Co-administrations of MenACWY + Tdap [11–13,23], and MenACWY + Tdap + HPV [24–27] were studied in four different trials each. Co-administrations of DTaP-HepB-IPV/Hib + PCV [9,28,29], DTaP-HepB-IPV/Hib + MMRV [30–32], and MMR + VAR [33–35] were studied in three different studies each. Co-administrations of MenACWY + DTaP-HepB-IPV/Hib [36,37], DTaP-IPV/Hib + MMR [16,32], HPV + HepB [38,39], and IIV (H1N1) + IIV3 [40,41] were each evaluated in two studies.

We only found statistically significant differences between co-administration and separate administration for some AEFI, and for a limited number of vaccine co-administrations. Furthermore, multiple studies on the same co-administered vaccines did not confirm each other's findings, as indicated in Table 2. Despite much more injection site bruising and slightly more injection site pain after co-administering MenACWY + Tdap + HPV found in one study [11], three other studies evaluating the same co-administered vaccines [12,13,23] could not confirm this increase. On the other hand, one of these studies detected an increase in myalgia after co-administering MenACWY + Tdap + HPV [13] but the three similar studies did not [11,12,23]. Likewise, only one of these studies found an increase of injection site swelling after co-administration [12] in contrast to the others [11,13,23]. Nevertheless, the incidence rates of these adverse events were in line with those reported in a study investigating the co-administration of MenACWY + Tdap + HPV but without a separate administration control group [42]. Similarly, only one of three studies on DTaP-HepB-IPV/Hib + PCV7 found a strong increase in cases of pyrexia after co-administration [9,28,29]. Also, here the incidence rates of fever were comparable with those observed in six other studies investigating the co-administration of the same vaccines but without a separate administration control group [43–48]. The consistency in incidence rates indicates that the observations are reliable and that the failure to detect significant differences rather might be due to a lack of statistical power.

**Table 2.** Number of studies with statistically significant differences in AEFI after co-administration compared to separate administration.

| Vaccines Co-Administered | Number of Studies | AEFI | Stat. Sign. More AEFI | Stat. Sign. Fewer AEFI | No Stat. Sign. Difference |
|---|---|---|---|---|---|
| DTaP-HepB-IPV/Hib + MenC | 1 | Injection site erythema | 0 (0%) | 1 (100%) | 0 (0%) |
| DTaP-HepB-IPV/Hib + PCV7 | 3 | Pyrexia | 1 (33%) | 0 (0%) | 2 (67%) |
| DTaP-IPV + RV5 | 1 | Diarrhoea | 0 (0%) | 1 (100%) | 0 (0%) |
| | | Pyrexia | 0 (0%) | 1 (100%) | 0 (0%) |
| DTaP-IPV/Hib + MenC + RV | 1 | Vomiting | 1 (100%) | 0 (0%) | 0 (0%) |
| DTaP-IPV/Hib + MMR | 1 | Overall | 1 (100%) | 0 (0%) | 0 (0%) |
| MenACWY + Tdap + HPV | 4 | Injection site bruising | 1 (25%) | 0 (0%) | 3 (75%) |
| | | Injection site pain | 1 (25%) | 0 (0%) | 3 (75%) |
| | | Injection site swelling | 1 (25%) | 0 (0%) | 3 (75%) |
| | | Myalgia | 1 (25%) | 0 (0%) | 3 (75%) |
| MMR + VAR + Hib-HepB | 1 | Rash | 0 (0%) | 1 (100%) | 0 (0%) |
| | | Rhinorrhoea | 0 (0%) | 1 (100%) | 0 (0%) |
| OPV + LAIV | 1 | Conjunctivitis | 0 (0%) | 1 (100%) | 0 (0%) |
| PCV7 + MMRV | 1 | Insomnia | 0 (0%) | 1 (100%) | 0 (0%) |
| | | Nasopharyngitis | 0 (0%) | 1 (100%) | 0 (0%) |
| PCV13 + IIV3 | 1 | Pyrexia | 1 (100%) | 0 (0%) | 0 (0%) |
| Td + MMR + HepB | 1 | Headache | 1 (100%) | 0 (0%) | 0 (0%) |
| | | Injection site tenderness | 1 (100%) | 0 (0%) | 0 (0%) |

For the co-administered vaccines where only one study could be retrieved, almost three times more cases of injection site tenderness and almost four times more headaches were reported following co-administration of Td + MMR + HepB [14], more than twice as many cases of pyrexia were found after co-administering PCV13 + IIV3 [10], and twice as much vomiting was reported following co-administering DTaP-IPV/Hib + MenC + RV [15]. A smaller increase in overall adverse events following co-administration of DTaP-IPV/Hib + MMR was observed in the only study with these vaccines [16].

Some studies found fewer AEFI after co-administration compared to separate administration: Half the cases of diarrhea and half the cases of pyrexia following co-administration of DTaP-IPV + RV5 [17], less injection site erythema following DTaP-HepB-IPV/Hib + MenC co-administration [18], almost half as much rash and less rhinorrhea after MMR + VAR + Hib-HepB co-administration [19], almost half as much nasopharyngitis and less insomnia following co-administering PCV7 + MMRV co-administration [20], and less conjunctivitis after co-administering OPV + LAIV compared to separate administration [21]. All these co-administrations were assessed in only one study each.

Despite the few studies on the same co-administered vaccines, it is remarkable that none of the reported increased adverse events following co-administration were contradicted by another study that would report a significant decrease following the same co-administration, and vice versa. In general, the studies indicate differences in less severe AEFI. Therefore, these insights might not influence immunization practices that much (also because we have not addressed the potential impact of co-administration on efficacy in our review) but can be meaningful to correctly inform patients and parents.

The lack of repeated studies for the majority of vaccine co-administrations and the absence of confirmatory findings of significant results indicate a scarcity of strong evidence about the safety of co-administration versus separate administration. This lack of evidence can be partly explained by the inability to demonstrate statistically significant safety differences. Two-thirds of studies reported differences in safety between vaccine co-administration and separate administration but these were not significant or a statistical assessment was missing. Typically, safety was briefly described and one-third of studies lacked any statistical assessment of AEFI. Most of the studies were randomized clinical trials (RCTs) mainly designed to demonstrate efficacy, with sample sizes that were too small for assessing particularly rare and very rare adverse events with sufficient statistical power [49]. This may be a reason why studies failed to detect statistically significant differences in safety. Observational studies with larger sample sizes assessing co-administration versus separate administration have better potential to achieve sufficient statistical power. However, such studies were found to be rare. Publication bias towards publishing studies with a positive benefit–risk balance may also affect the availability of information on safety and hence affect the findings of our review. Studies with an unsatisfactory immunogenicity and/or an unfavorable safety profile might not have been published.

Our findings indicate that dedicated studies on vaccine co-administration with a larger sample size are required to obtain statistical evidence on a potential increase or decrease of adverse events following co-administration. Particularly for co-administered vaccines for which an increased or decreased risk compared to separate administration was observed, confirmatory studies specifically designed to assess the safety of co-administration would be useful. Such studies should aim at assessing AEFIs with sufficient statistical power and would benefit from standardized data collection of AEFIs and established methodologies for the assessment of adverse events following vaccine co-administration compared to separate administration.

## 5. Conclusions

Evidence about no increased risk of adverse events when co-administering vaccines compared to separate vaccine administration is indispensable to improve immunization rates. Opposition to vaccination and under-vaccination are crucial threats to herd immunity [50], which can be addressed by proving the safety of vaccine co-administration. Co-administration is an efficient vaccination strategy,

associated with high coverage rates [3] and vaccine timeliness [51]. While there is no indication to be concerned about the safety of co-administered vaccines, healthcare providers must aim for the highest standards of care. Particularly for preventive care in children such as immunization, we must aim for the best strategies that entail the lowest risks. Considering the scale of immunizing children and vaccine co-administrations in real life, the currently available evidence is limited and inconclusive. This study indicated that differences in safety of vaccine co-administrations compared to separate vaccine administrations may exist, particularly for more common, less severe AEFI. However, based on the currently available evidence, it is challenging to verify the true extent and impact. In summary, there is limited and inconclusive evidence available about the difference in safety of vaccine co-administrations compared to separate vaccine administrations in children.

**Supplementary Materials:** The following are available online at http://www.mdpi.com/2076-393X/8/1/12/s1, Table S1: Characteristics of studies comparing co-administration versus separate administration. Table S2: List of abbreviations.

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# Manuscript 2: **Adherence to the paediatric immunisation schedule in England**

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# Adherence to the paediatric immunisation schedule in England

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ABSTRACT

Both adequate coverage and adherence to paediatric immunisation schedules are required for optimal protection against vaccine preventable diseases. We studied the timeliness of routine paediatric vaccinations according to the NHS's immunisation schedule and potential factors of schedule adherence. Immunisation data was obtained from the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC). We collected vaccine types, doses, and dates for all routine paediatric vaccines 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. Adherence to the immunisation schedule was calculated for each vaccine and dose. Differences in adherence between genders, NHS regions, and IMD quintiles were analysed. Our study included 6′257′828 vaccinations in 1′005′827 children. Seventy-five percent of first doses were administered within one (for vaccines scheduled in the first year of life) or two months (for vaccines scheduled later in life) following the recommended age, 19% too late and 6% too early. About half of the subsequent doses were given timely. The time between first and second doses was too short for 36% of vaccinations while 13% of second doses were administered too long after the first dose. Third doses were administered timely for 45%, too short for 37%, and too long for 18% of vaccinations. Differences in immunisation schedule adherence between girls and boys were negligible, except for HPV, and differences between the four main NHS regions were small. Overall, immunisation schedule adherence improved slightly with decreasing deprivation according to the Index of Multiple Deprivation. Efforts are required to improve the timeliness of paediatric vaccinations and to assure adequate protection against vaccine preventable diseases. We propose developing a compound measure combining coverage and adherence to provide a better indication of the protection against vaccine preventable diseases in a community.


## 1. Introduction

Both coverage and adherence to paediatric immunisation schedules are essential to assure optimal protection against vaccine preventable diseases early in life. Routine paediatric vaccination coverage rates in England between 2008 and 2018 varied between vaccines, ranging from the lowest for measles-mumps-rubella vaccine (MMR) with 78% in 2008–2009 [1] and the highest for diphtheria-tetanus-pertussis-poliovirus-*Haemophilus influenzae* b vaccine (DTaP/IPV/Hib) with 95% in 2012–2013 [2]. However, high coverage rates may overestimate protection when adherence to the immunisation schedule - i.e. the timeliness of vaccinations - is low [3]. Despite high vaccination coverage, non-adherence to the recommended immunisation schedule may jeopardise the intended protection by vaccination. Late vaccinations may leave a child vulnerable to vaccine-preventable diseases for a longer than intended period, while vaccines received earlier or at shorter intervals than recommended may lead to a suboptimal immune response and a false sense of protection [3–5].

The National Health Services (NHS) and Public Health England's immunisation schedule for 2018 recommended 19 vaccinations (first and subsequent doses) for 17 different antigens, at eight moments between birth and 14 years (Fig. 1) [6]. Nevertheless, actual vaccine administration might not happen according to the

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**Nomenclature**

| Abbreviation | Meaning |
|---|---|
| *Vaccines:* | |
| DTaP/HepB/IPV/Hib | Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B, inactivated poliovirus, and *Haemophilus influenzae* type b conjugate vaccine |
| DTaP/IPV/Hib | Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, and *Haemophilus influenzae* type b conjugate vaccine |
| DTaP/IPV or dTaP/IPV | Diphtheria and tetanus toxoids and acellular pertussis adsorbed, and inactivated poliovirus vaccine |
| HepB | Hepatitis B vaccine |
| Hib/Men | *Haemophilus influenzae* type b conjugate, and bivalent meningococcal conjugate vaccine |
| HPV | Human papillomavirus vaccine |
| MenACWY | Quadrivalent meningococcal conjugate vaccine |
| MenB | Serogroup B meningococcal vaccine |
| MenC | Serogroup C meningococcal vaccine |
| MMR | Measles, mumps, and rubella vaccine |
| PCV | Pneumococcal conjugate vaccine |
| RV | Rotavirus vaccine |
| Td/IPV | Tetanus and diphtheria toxoids and inactivated poliovirus vaccine |
| *Terms*: | |
| GP | General Practitioner |
| IMD | Index of Multiple Deprivation |
| IQR | Interquartile Range |
| OR | Odds Ratio |
| RCGP | Royal College of General Practitioners |
| RSC | Research and Surveillance Centre |

schedule for various reasons. Insight in non-adherence to vaccination schedules is essential to inform measures to improve adherence to vaccination schedules. This will eventually improve protection against vaccine preventable diseases in the population and minimise the risk of adverse events. Our study assessed the timeliness of routine paediatric vaccinations according to the NHS' immunisation schedule, and explored potential factors of adherence to the schedule.

## 2. Methods

We extracted data from the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), a national, electronic primary health care medical record database in England, managed by the Clinical Informatics and Health Outcome Research Group at University of Surrey [7]. The RCGP RSC comprises patient data from over 100 participating general practices across England and a recent cohort profile of this database demonstrated it is representative for the English population [8].

Our cohort study included all children who were between 0 and 18 years old during the study period from 1 January 2008 to 31 December 2018, and received a routine paediatric vaccine. Children were excluded from analyses if they were registered in the database after the scheduled age for the first dose of a vaccine. Children's birthdays recorded in the database were limited to month and year of birth. Therefore, birthdates were rounded to the first of the month in the analysis. Every child in the database had a unique, anonymised identifier. For each child, we also collected the gender, the NHS-region of residence in England (North England; Midlands and East England; London; South England), and the postcode-based Index of Multiple Deprivation (IMD) quintiles (1 being most deprived, 5 being least deprived) [9].

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 [6,10–17]. Tuberculosis and HepB vaccinations were only recommended for children with underlying medical conditions and excluded from analysis. Influenza vaccines and any vaccines that were not listed on the paediatric immunisation schedules at any time during the study period were also excluded. Dose numbers were assigned based on the chronological sequence of administration for each vaccine type.

The recommended age for immunisation was determined by the age listed in the immunisation schedule that was valid at the time of vaccination (see Table 1). We defined vaccination "within

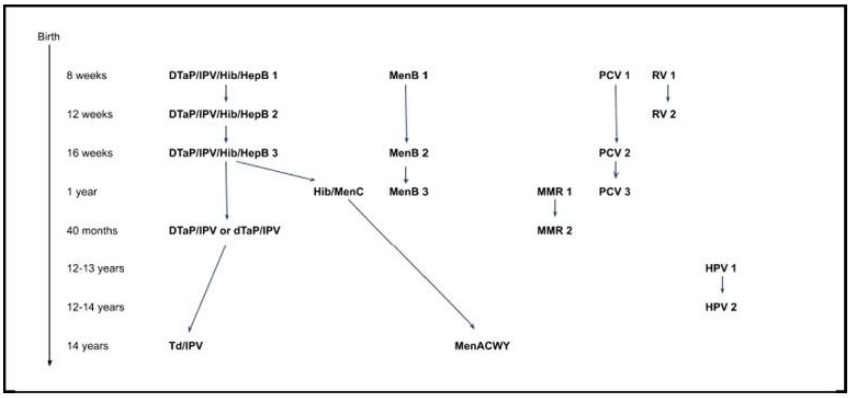


**Fig. 1.** Routine paediatric immunisation schedule NHS 2018 [6].

1 month following recommended age" when a scheduled first dose of a vaccine was received at the recommended age or within one month thereafter for vaccines scheduled in the first year of life, or vaccination "within 2 months following recommended age" for vaccines received at the recommended age or within 2 months thereafter for first doses scheduled later in life.

The recommended age for first doses was calculated as a time range, reflecting that birth dates were rounded to the first day of the month in the database: the first day of the window assuming a child born on the first day of the given month and the last day of the window assuming a child born on the last day of the given month. The recommended time intervals between subsequent doses were defined by the difference in age between doses according to the immunisation schedule valid at the time of vaccination. Vaccination "within 1 month following recommended interval" was defined as having received the subsequent dose at the recommended time interval or within one month thereafter for doses scheduled in the first year of life, or "within 2 months following recommended interval" for subsequent doses received within 2 months after the recommended time interval for doses scheduled later in life. The applied time windows were determined based on paediatricians' feedback about real-life immunisation practices, immunisation guidelines, literature indicating that immunisations within one month after the recommended age are not uncommon and tolerated [18–22], and correspond to time windows used in similar studies [23–29].

Any vaccines given before the scheduled age were considered early and those after the scheduled age plus the defined windows late. Subsequent doses given within a shorter period than recommended by the immunisation schedule were classified as a too short gap, or when given beyond the scheduled gap plus the defined window as a too long gap. We only included vaccines administered and did not consider missed vaccinations.

Timeliness of vaccination according to the immunisation schedule was calculated for each vaccine and dose as the proportion of children who received the vaccine within the determined time windows. For each vaccine and dose, deviation from the scheduled age or gap was calculated as the number of months a vaccine was given before or after the defined time windows. Also the distribution of all vaccinations around their time windows was assessed. We analysed differences in timeliness between genders, NHS regions, and IMD quintiles for each vaccine and dose using

**Table 1**
Scheduled ages, gaps, and time windows applied in this study.

| Vaccine and dose | Scheduled age | Scheduled gap following preceding dose | Maximum age/gap applied |
|---|---|---|---|
| DTaP/IPV/Hib/HepB 1 | 8 weeks | – | 12.3 weeks |
| DTaP/IPV/Hib/HepB 2 | 12 weeks | 4 weeks | 8.3 weeks |
| DTaP/IPV/Hib/HepB 3 | 16 weeks | 4 weeks | 8.3 weeks |
| DTaP/IPV/Hib 1 | before 2016: 2 months<br>since 2016: 8 weeks | – | before 2016: 3 months<br>since 2016: 12.3 weeks |
| DTaP/IPV/Hib 2 | before 2016: 3 months<br>since 2016: 12 weeks | before 2016: 1 month<br>since 2016: 4 weeks | before 2016: 2 months<br>since 2016: 8.3 weeks |
| DTaP/IPV/Hib 3 | before 2016: 4 months<br>since 2016: 16 weeks | before 2016: 1 month<br>since 2016: 4 weeks | before 2016: 2 months<br>since 2016: 8.3 weeks |
| DTaP/IPV 1 or dTaP/IPV | 2009–2011: 40–60 months<br>since 2011: 40 months | – | 2009–2011: 61 months<br>since 2011: 41 months |
| Td/IPV 1 | before 2009: 13–18 years<br>2009–2011: 15 years<br>2011–2013: 13–18 years<br>since 2013: 14 years | – | before 2009: 18 years + 1 month<br>2009–2011: 15 years + 1 month<br>2011–2013: 18 years + 1 month<br>since 2013: 14 years + 1 month |
| MMR 1 | until 2009: 13 months<br>2009–2011: 15 months<br>2011–2016: 12–13 months<br>since 2016: 1 year | – | until 2009: 14 months<br>2009–2011: 16 months<br>2011–2016: 14 months<br>since 2016: 1 year + 1 month |
| MMR 2 | 2009–2011: 40–60 months<br>since 2011: 40 months | until 2009: 17 months<br>2009–2011: 25–45 months<br>2011–2016: 27–28 months<br>since 2016: 28 months | until 2009: 18 months<br>2009–2011: 46 months<br>since 2011: 29 months |
| PCV 1 | before 2016: 2 months<br>since 2016: 8 weeks | – | before 2016: 3 months<br>since 2016: 12.3 weeks |
| PCV 2 | before 2016: 4 months<br>since 2016: 16 weeks | before 2016: 2 months<br>since 2016: 8 weeks | before 2016: 3 months<br>since 2016: 12.3 weeks |
| PCV 3 | until 2009: 13 months<br>2009–2011: 15 months<br>2011–2016: 12–13 months<br>since 2016: 1 year | until 2009: 9 months<br>2009–2011: 11 months<br>2011–2016: 8–9 months<br>since 2016: 36 weeks | until 2009: 10 months<br>2009–2011: 12 months<br>2011–2016: 10 months<br>since 2016: 40.3 weeks |
| MenB 1 | 8 weeks | – | 12.3 weeks |
| MenB 2 | 16 weeks | 8 weeks | 12.4 weeks |
| MenB 3 | 1 year | 36 weeks | 40.3 weeks |
| MenC 1 | 3 months | – | 4 months |
| MenC 2 | before 2013: 4 months<br>since 2013: 14 years | before 2013: 1 month<br>since 2013: 13 years + 9 months | before 2013: 2 months<br>since 2013: 13 years + 10 months |
| MenACWY | 14 years | – | 14 years + 1 month |
| Hib/MenC 1 | until 2011: 12 months<br>2011–2016: 12–13 months<br>since 2016: 1 year | – | until 2011: 13 months<br>2011–2016: 14 months<br>since 2016: 1 year + 1 month |
| Rotavirus 1 | before 2016: 2 months<br>since 2016: 8 weeks | – | before 2016: 3 months<br>since 2016: 12.3 weeks |
| Rotavirus 2 | before 2016: 3 months<br>since 2016: 12 weeks | before 2016: 1 month<br>since 2016: 4 weeks | before 2016: 2 months<br>since 2016: 8.3 weeks |
| HPV 1 | 12–13 years | – | 13 years + 1 month |
| HPV 2 | 12–14 years | – | 14 years + 1 month |

Pearson's chi-square test and logistic regression, as well as the impact of the timeliness of preceding doses on the timeliness of subsequent doses. We used a significance level of 0.05 to determine whether on vaccination within 1 month (for doses scheduled in the first year of life) or 2 months (for doses later in life) following the recommended time 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. All analyses were performed in R [30].

## 3. Results

We analysed 6′257′828 vaccine jabs, covering 15′182′366 antigens, in 1′005′827 children meeting our inclusion criteria. The study population was representative for the entire population in the database (see Table 2). Twenty percent of children received all their vaccines within the defined time windows.

Overall, 75% of first doses were administered on the scheduled age or within one month thereafter , 19% more than one month too late and 6% before the scheduled age (too early). The medians for deviations from the schedule varied between 0 and 1 month (IQR 0 and 2 months), except for DTaP/IPV or dTaP/IPV (median 2 months; IQR 0 to 5), Td/IPV (median 1 month; IQR −1 to 13), and MenACWY (median 29 months; IQR 6 to 55). The time windows between first and second doses were respected in 51% of vaccinations. The medians for deviations from the scheduled time between doses varied between 0 and 1 month, with an IQR between −2 and 2 months. The period between the first and second dose was too short for 36% of vaccinations while 13% of second doses were administered too long after the first dose. Third doses were administered within the defined time windows after a second dose for 45%, too short for 37%, and too long for 18% of vaccinations. Receiving a preceding dose late significantly increased the odds on a too short gap until receiving the subsequent dose of the same vaccine (OR 1.8). Figs. 2 and 3 illustrate the deviation from the immunisation schedule for each of the included vaccines, Figs. 4 - 9 demonstrate the differences in adherence to the immunisation schedule for each of the included vaccines between gender, NHS regions, and IMD quintiles, while Table 3 presents the odds ratios of vaccinations within the defined time windows for these factors per vaccine.

### 3.1. DTaP vaccines

DTaP/IPV/Hib/HepB replaced DTaP/IPV/Hib on the immunisation schedule in spring 2018. Ninety-two percent of the first DTaP/IPV/Hib doses and 93% of the first DTaP/IPV/Hib/HepB doses were administered within 1 month following the recommended age. Forty-nine percent of subsequent DTaP/IPV/Hib doses were administered within 1 month following the recommended interval, while 42% were administered within a shorter period. Subsequent DTaP/IPV/Hib/HepB doses were given within 1 month following the recommended interval in 92%. Timeliness of administration for DTaP/IPV/Hib and DTaP/IPV/Hib/HepB vaccines significantly increased with decreasing deprivation (Figs. 8 and 9). Timeliness of administration was most likely in North England for both vaccines' first doses and the least likely in London for the first dose of DTaP/IPV/Hib and all doses of DTaP/IPV/Hib/HepB. Subsequent doses in London were more often given later than in the other regions. Subsequent doses of DTaP/IPV/Hib/HepB were given clearly more timely in the South of England and subsequent doses of DTaP/IPV/Hib more timely in the Midlands and East-England (Figs. 6 and 7). The timeliness of the first dose of DTaP/IPV/Hib was similar for boys and girls.

Fifty-five percent of DTaP/IPV and dTaP/IPV vaccines (scheduled at 40 months) were given within 2 months following the recommended age and 39% too late. A small peak of early administrations was seen around three months of age. Td/IPV vaccines, scheduled at the age of 14 since 2013, were given within 2 months following the recommended age in 28%, while 46% of vaccines were administered too late. Timeliness increased with decreasing deprivation (Fig. 8). Schedule adherence was clearly less likely in London and most likely in South England for DTaP/IPV and dTaP/IPV vaccines (OR: 2.1) and in North England for Td/IPV (OR: 1.7). Boys were slightly more likely to receive DTaP/IPV and dTaP/IPV vaccines within 2 months following the recommended age (OR: 1.1).

### 3.2. Meningitis vaccines

Ninety percent of the first MenB vaccines were administered within 1 month following the recommended age and 10% too late, with a small peak almost one year later, around the scheduled age for the third dose at the age of one. Eighty-one percent of the second MenB vaccine doses and 45% of the third doses were administered within 1 month following the recommended interval. Five percent of the second doses were given too soon and 15% too long after the first dose, while 35% of third doses were given too soon and 20% too long after the second dose. MenB vaccine was less likely to be administered timely in London and more likely in North England (Table 3). The least deprived areas accounted for the lowest timeliness and also more late administrations for the

**Table 2**
Key variables study sample compared to population in database.

| | Immunisations | | | | Children | | | |
|---|---|---|---|---|---|---|---|---|
| | Sample | | Database | | Sample | | Database | |
| | n | % | N | % | n | % | n | % |
| Total | 6,257,828 | 100 | 8,083,825 | 100 | 1,005,827 | 100 | 1,149,892 | 100 |
| **Gender** | | | | | | | | |
| Female | 3,316,654 | 53.0 | 4,260,954 | 52.7 | 554,218 | 55.1 | 613,028 | 53.3 |
| Male | 2,941,174 | 47.0 | 3,822,871 | 47.3 | 451,609 | 44.9 | 536,864 | 46.7 |
| **Region** | | | | | | | | |
| London | 1,230,368 | 19.7 | 1,569,082 | 19.4 | 182,774 | 18.2 | 207,922 | 18.1 |
| Midlands and East | 1,063,025 | 17.0 | 1,379,538 | 17.1 | 168,861 | 16.8 | 193,846 | 16.9 |
| North | 1,945,646 | 31.1 | 2,503,791 | 31.0 | 318,034 | 31.6 | 365,689 | 31.8 |
| South | 2,018,789 | 32.3 | 2,631,414 | 32.6 | 336,158 | 33.4 | 382,435 | 33.3 |
| **IMD** | | | | | | | | |
| 1 | 1,163,036 | 18.9 | 1,490,016 | 18.8 | 182,923 | 18.5 | 210,269 | 18.7 |
| 2 | 1,128,030 | 18.4 | 1,454,788 | 18.3 | 179,850 | 18.2 | 206,181 | 18.3 |
| 3 | 1,135,039 | 18.5 | 1,460,684 | 18.4 | 181,663 | 18.4 | 208,307 | 18.5 |
| 4 | 1,257,428 | 20.5 | 1,627,364 | 20.5 | 204,479 | 20.7 | 233,233 | 20.7 |
| 5 | 1,457,420 | 23.7 | 1,900,810 | 24.0 | 237,484 | 24.1 | 268,885 | 23.9 |

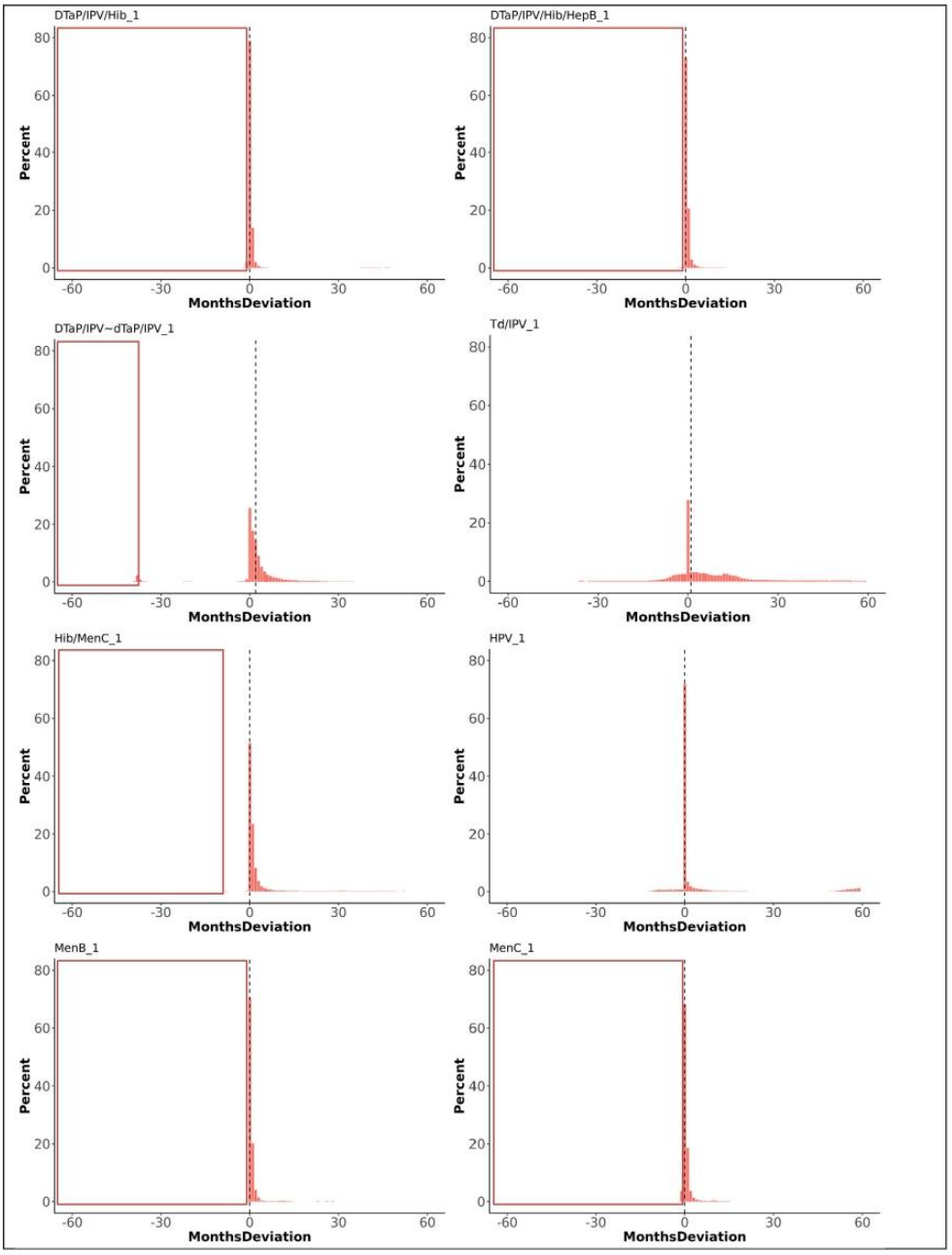


**Fig. 2.** Deviations from the scheduled vaccination age for first doses, in months (dotted line indicates median deviation; red frames indicate invalid vaccinations requiring reimmunisation). The graphs present the proportions of vaccines administered at, before, or after the recommended age. Deviations from the schedule are categorised by the number of months before (negative numbers) or after (positive numbers) the recommended age. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

first dose of MenB vaccine, while timeliness for the subsequent doses improved with decreasing deprivation (Figs. 8 and 9). The timeliness of the second dose of MenB vaccine was similar for girls and boys.

Eighty-four percent of MenC vaccines dose 1 were administered within 1 month following the recommended age, and 13% too late. The second dose of MenC vaccine was given within 1 month following the recommended interval for 40% of vaccinations, too soon

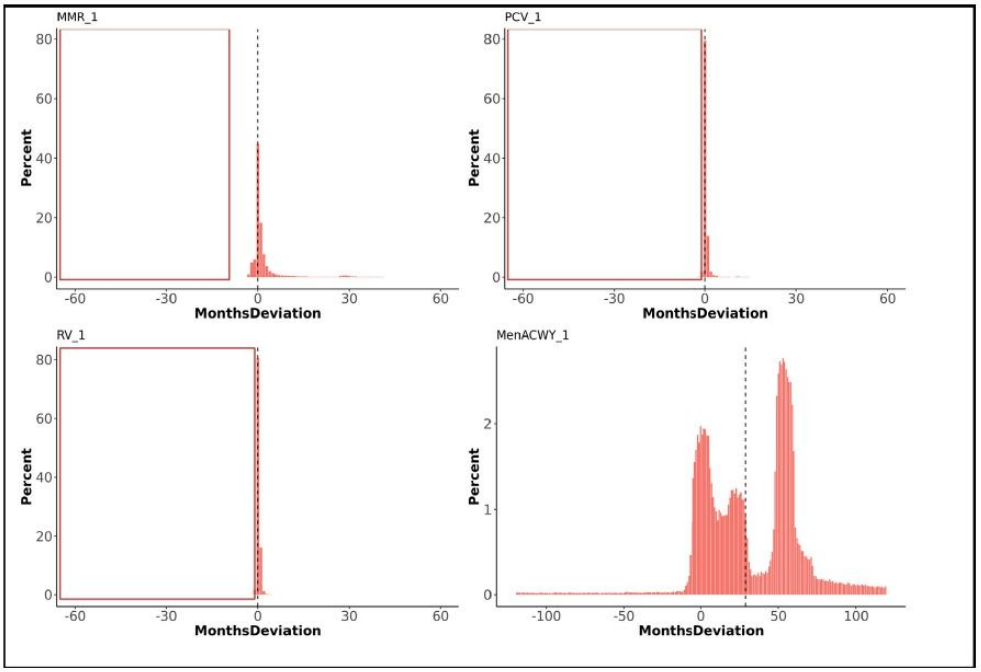


**Fig. 2** (*continued*)

after the first dose for 50% - all within one month of the recommended gap - and too long for 10% of vaccinations. Timeliness for both doses of MenC vaccine improved with decreasing deprivation (Figs. 8 and 9). We found the highest likeness for timeliness in the Midlands and East England for both doses (Table 3) versus the lowest in London for the first dose and in North England for the second dose. The timeliness of the first MenC dose was similar for both genders.

Thirteen percent of children received the MenACWY vaccine before the scheduled age of 14, while 81% percent received the vaccine more than 2 months after their 14th birthday. The mean delay was 29 months, with an IQR between 6 and 55 months. Boys were slightly more likely to receive the vaccine within 2 months following the recommended age than girls (OR: 1.2). The vaccine was given the least timely and most early in London, and clearly more timely in South-, Midlands and East-England (OR: 2.3 and 2.4).

Hib/MenC was administered within 1 month following the recommended age for 83% of vaccinations and too late for 17%. Adherence was least likely in London and most likely in the Midlands and East-England (OR: 1.6). The reported timeliness increased clearly with decreasing area deprivation (Fig. 8).

### 3.3. MMR vaccines

Sixty-nine percent of MMR vaccine first doses were administered within 1 month following the recommended age, 20% too late and 11% too early. Although most doses were distributed around the scheduled age, we found a small peak of first doses around the age where the second dose was scheduled. Thirty percent of the second MMR vaccine doses were given within 2 months following the recommended interval after the first dose, 46% were given too short and 24% too long after the first dose. We observed a small trend of second doses given within a few months after the first dose instead of 28 months later. Timeliness was the worst in London, particularly for the second dose of MMR vaccine. More first doses were given late and the second doses too shortly after the first one in London. Adherence to the immunisation schedule was most likely in the Midlands and East-England (OR: 1.3 for the first and 3.5 for the second dose). Timeliness clearly increased with decreasing area deprivation.

### 3.4. PCV vaccines

Ninety-three percent of the first PCV vaccine doses were given within 1 month following the recommended age and five percent too late. Timeliness decreased with subsequent doses that were given within 1 month following the recommended interval on average for 48% of vaccinations, too short after the preceding dose for 33% and too long for 20% of subsequent doses. Timeliness improved for all doses with decreasing area deprivation. PCV vaccines were most likely given timely in the Midlands and East-England and the least in London (Table 3).

### 3.5. RV vaccines

The proportions of RV vaccinations given within 1 month following the recommended time dropped from 97% for the first dose to 63% for the second dose. Thirty-two percent of second doses were given too long after the first dose. Timeliness of the first dose slightly improved with decreasing deprivation. Adherence was most likely in the Midlands and East-England (OR: 1.5) and the least in London.

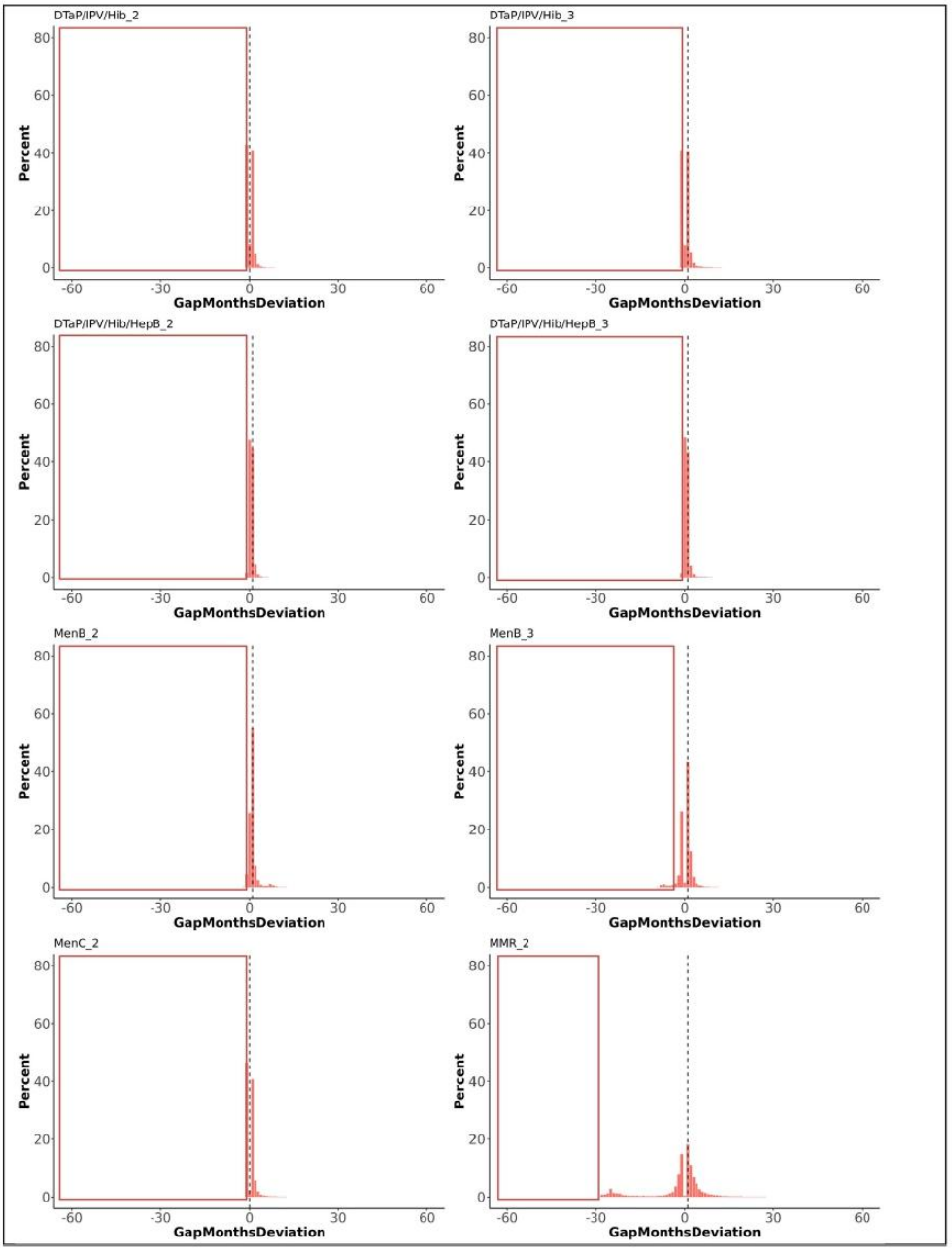


**Fig. 3.** Deviations from the scheduled gap between doses, in months (dotted line indicates median deviation; red frames indicate invalid vaccinations requiring reimmunisation). The graphs present the proportions of vaccines administered at, before, or after the recommended age. Deviations from the schedule are categorised by the number of months before (negative numbers) or after (positive numbers) the recommended age. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

### 3.6. HPV vaccines

The first and second doses of HPV vaccine were given within 2 months following the recommended age for 73% and 74% of the respective vaccinations. Twenty percent of both doses were given too late and 6% too early. Boys were significantly less likely to receive the HPV vaccine timely (Table 3). Forty-nine percent received dose 1 later than the recommended age and 40% received

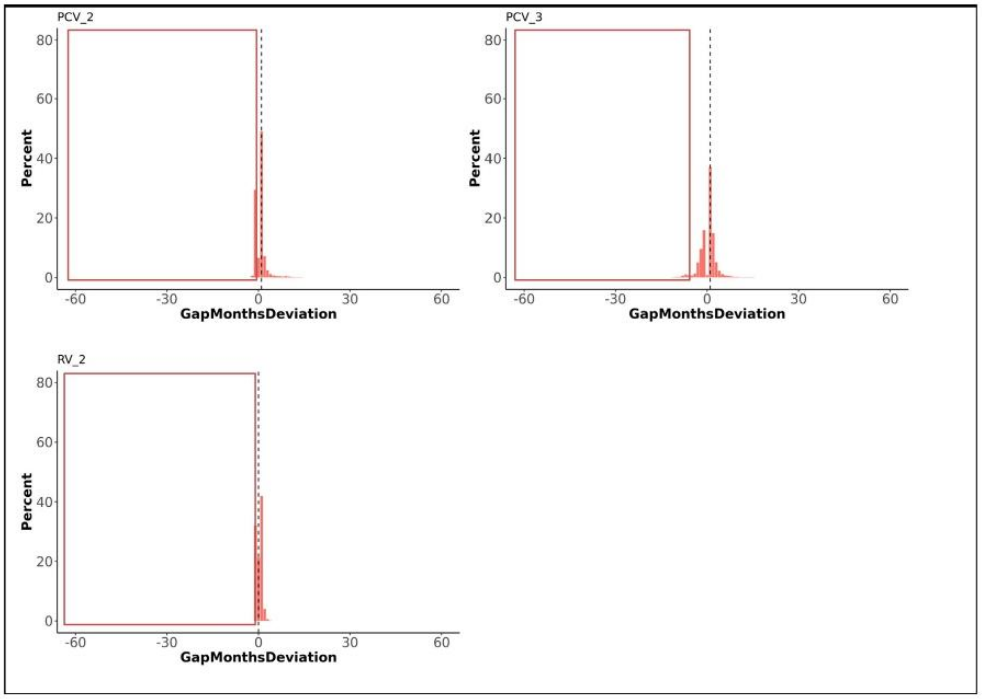


**Fig. 3** (*continued*)

dose 2 later. Adherence was least likely in London and most likely in South England (Table 3). For both doses, we observed a small distribution of late vaccinations around 18 years of age.

## 4. Discussion

The timeliness of immunisation was better for routine paediatric vaccines scheduled in the first year of life and decreased for vaccines scheduled at older ages. Overall, three quarters of first doses were administered within 1 month (for vaccines scheduled in the first year of life) or 2 months (for vaccines scheduled later in life) following the recommended age while too early administrations of first doses were rare. Almost half of subsequent doses were not given timely after the preceding dose, particularly too shortly after the preceding dose. This can be partly explained by having received a prior dose later than scheduled but the subsequent dose at the scheduled age. Our findings confirm previous studies with smaller study populations that also reported high timeliness, up to 95%, of first vaccine doses scheduled in the first year of life, with a decreasing trend for subsequent doses and vaccines given after the age of 1, and proportions between 22% and 87% of children with at least one delayed vaccination compared to 80% in our study [5,23–29,31–34].

Immunisation schedule adherence was similar for girls and boys, and differences between the four main English regions were small. Other studies found that the organisation of health care and health systems affect vaccination timeliness [35,36]. Having one health care system in place all over England might explain the absence of large differences between regions. Nevertheless, immunisation schedule adherence was significantly less likely in London for almost all vaccines, while it was generally the highest in the Midlands and East England. Tiley et al. [31] found heterogeneity in paediatric vaccination timeless across ethnicities in London, which might negatively affect the overall adherence rate.

Immunisation schedule adherence improved slightly but significantly with decreasing deprivation for almost all vaccines. This corresponds with other studies reporting a negative association between deprivation and vaccination timeliness or finding that children in families living below the poverty level are less likely to follow recommended immunisation schedules and have up-to-date vaccinations [4,28,31,37]. Since routine paediatric vaccines are provided for free in England, this is not an issue of lacking financial means to pay for vaccinations, but might be related to other factors that are associated with poor health care service utilisation often seen with lower income families [38].

The timeliness of subsequent DTaP/IPV/Hib/HepB doses clearly improved compared to the timeliness of subsequent DTaP/IPV/Hib doses. Subsequent doses of DTaP/IPV/Hib were often administered too early (42%), similarly to subsequent doses of other vaccines. Too early administrations of subsequent DTaP/IPV/Hib/HepB doses accounted for 2% while doses given within 1 month following the recommended interval represented 92%. This may be due to the recent introduction of DTaP/IPV/Hib/HepB in the immunisation schedule [17]. Other studies documented improved timeliness following the introduction of new vaccines to the immunisation schedule [39,40] which may be explained by accompanying campaigns to assure that health care providers are well aware of recently published guidelines.

Although the MenACWY vaccine was scheduled at the age of 14, we observed that the vaccine was given between 14 and 16 years of age, or around the age of 18 years. This may be due to the recent

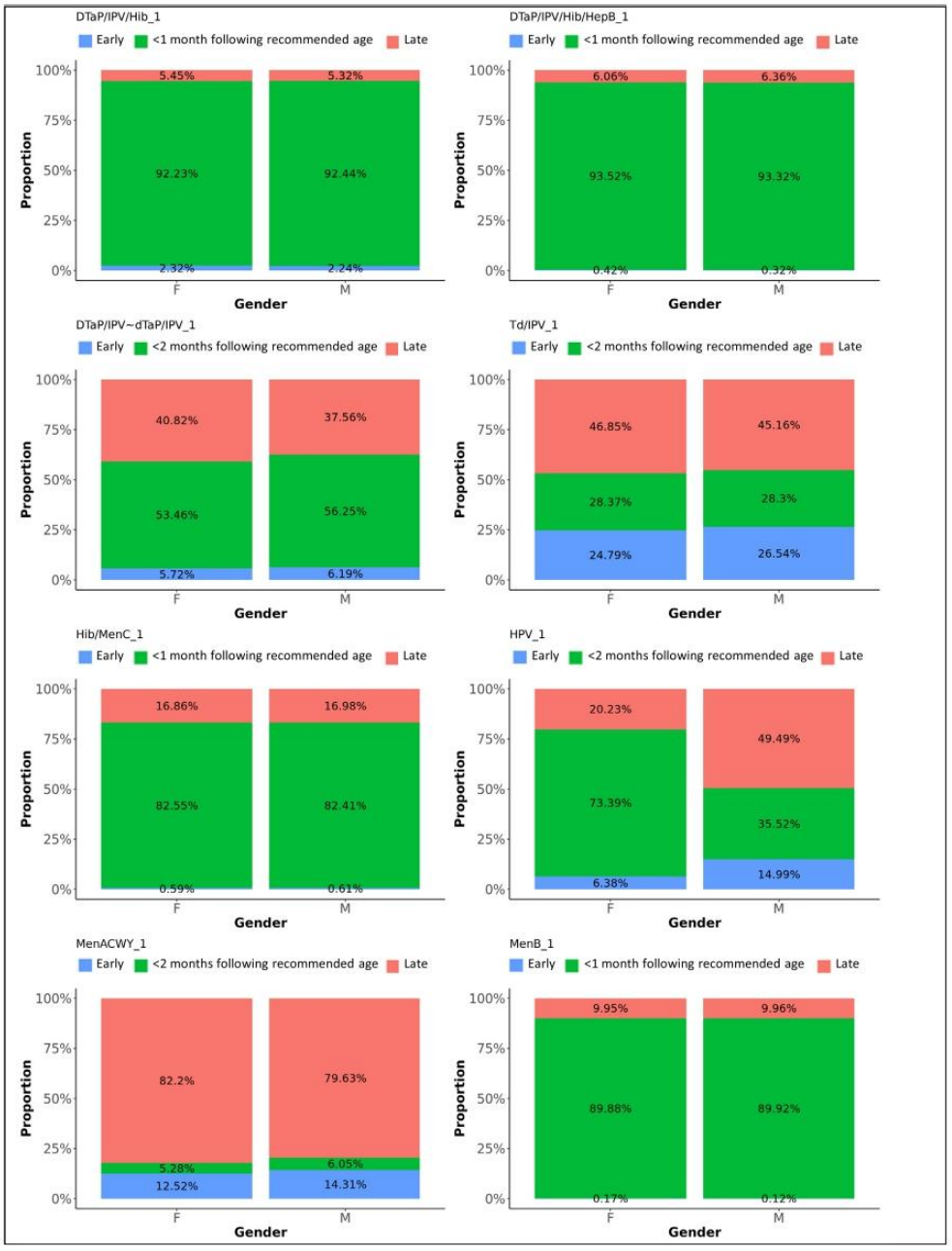


**Fig. 4.** Difference in adherence between genders, for first doses. The graphs present the proportions of each vaccine's first dose administered early, within 1 month following the recommended age for vaccines scheduled in the first year of life, or within 2 months following the recommended age for vaccines scheduled later in life (see Table 1), or late, for each gender.

introduction of the vaccine in 2016. Children who already passed their 14th birthday when the MenACWY vaccine was introduced, were still eligible to receive the vaccine, up to an age of 25 years. [41] This would explain why many children older than 14 received the vaccine. Since our study covers only the three first years of MenACWY being listed in the immunisation schedule, the proportion of children that received these catch up vaccinations would be relatively large but can be expected to decrease in future years.

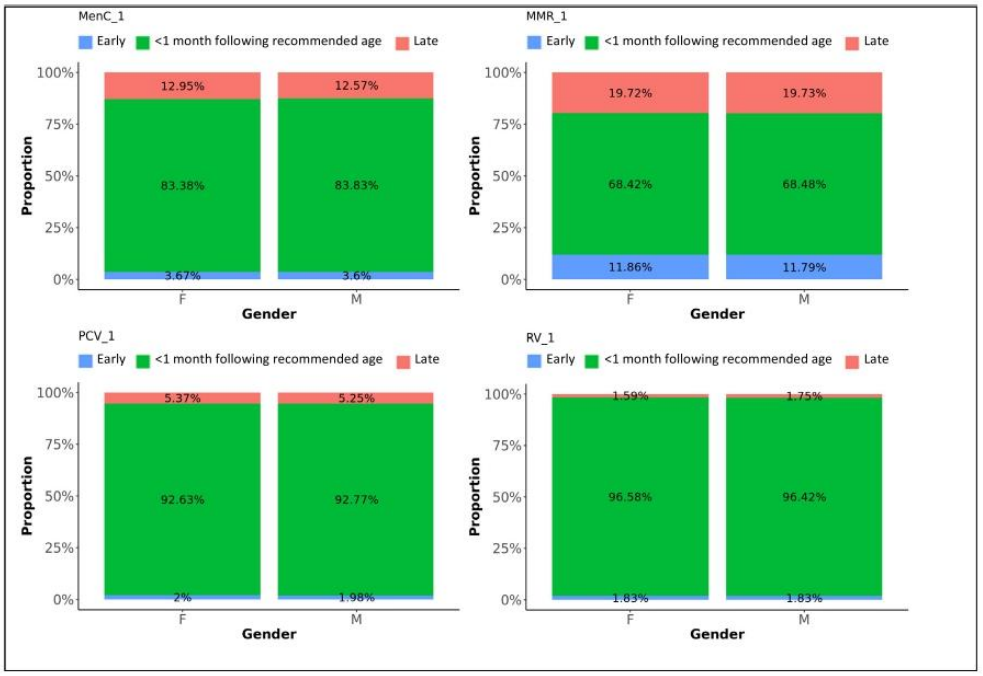


**Fig. 4** (*continued*)

The large sample size and the use of real practice data are strengths of our study. However, data is not collected for this specific study and entered by different persons and institutions, which may negatively impact the quality of the data. As a result, our data may be prone to misclassification and missingness due to wrong or incomplete information entered in medical records. When relying on existing medical records, analyses are restricted to the available variables captured in the database [42]. Therefore, we could not examine other potential factors than those discussed above. Only birth months and years are available in the database to guarantee anonymity. The absence of exact birth dates created some imprecision in calculating the exact age at immunisation for first doses. Therefore, we used rather wide acceptability windows for timeliness. This less stringent criterion for adherence contributes to higher adherence rates. For vaccines scheduled at 2 months or 8 weeks (the first doses of DTaP/IPV/Hib/HepB, DTaP/IPV/Hib, PCV, MenB, RV), we cannot exclude that immunisations that happened within 2 weeks before the minimum age of 6 weeks were classified as timely due to the lack of exact birth dates. For the other vaccines and doses included in our study, the acceptability windows don't exceed the minimum ages listed in immunisation guidelines [19,20,43]. Since the RCGP RCS database only collects data from GP practices, we could not track vaccinations at other healthcare facilities. However, routine childhood vaccines are typically given by GPs [44]. Children may have left the database during the study period. As a result, vaccinations these children may have received after leaving the database are not included in our analyses. Our analyses are also subject to right censoring: particularly for children born closer to the end of the study period, too late vaccinations that occurred after the study period could not be considered. Similarly left censoring occurred for children born close to the beginning of the study period, whose too early vaccinations may be missed.

Our study did not reveal major factors for poor vaccine schedule adherence. Both coverage and the timeliness of vaccinations are influenced by diverse factors interacting in complex ways [32]. Access to vaccinations and information about vaccinations raise vaccination coverage and timeliness [45] and also introducing new vaccines may improve vaccine coverage and timeliness [39,40]. Vaccine hesitancy can lead to refusing and delaying vaccinations [46]. This hesitancy can be constituted by contextual influences including historic, socio-cultural, environmental, health system/institutional, economic, or political factors; individual perceptions and group influences; or concerns directly related to vaccines as discussed by MacDonald [46].

The overall timeliness of vaccinations is suboptimal, particularly for subsequent doses and vaccines scheduled after the first year of life. While first doses are scheduled to protect children as early in life as possible, or at least before potential exposure to pathogens happens, the time between doses is determined to assure that an adequate and long lasting immunity is induced. [47] Subsequent doses given at shorter than recommended intervals may induce a reduced immune response and less durable protection, and reimmunisation is required when the interval is below the minimum interval (4 weeks for inactivated and life attenuated vaccines, 8 weeks for MenB and PCV) [48,49]. Although delayed doses still achieve the desired immunity [48,49], longer intervals between subsequent doses leave children suboptimally protected. Hence, any deviation from scheduled ages or intervals between vaccinations potentially undermines both personal and herd immunity. Therefore, interventions to improve vaccination coverage should also address the timeliness of vaccinations. Such

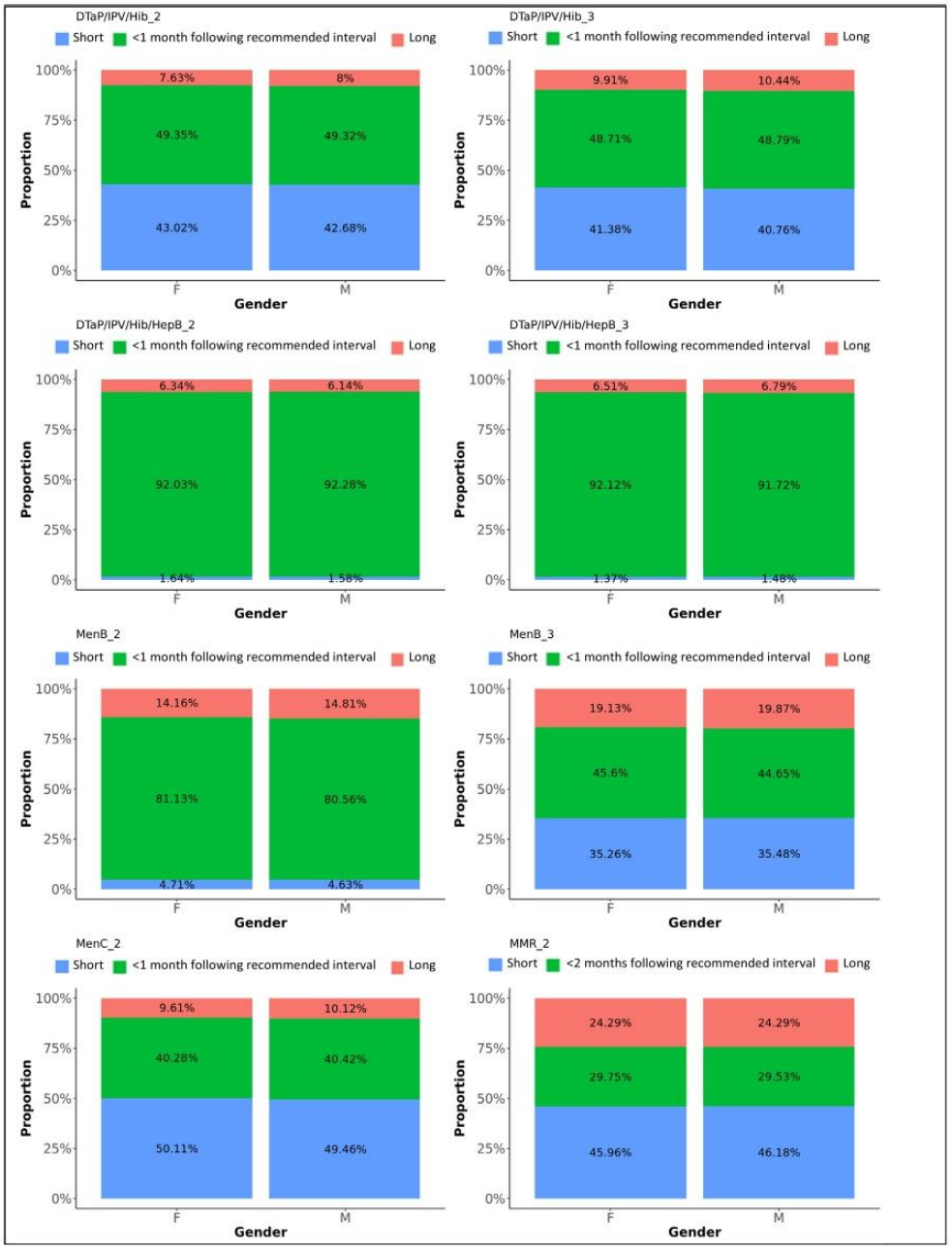


**Fig. 5.** Difference in adherence between genders, for subsequent doses. The graphs present the proportions of each vaccine's subsequent dose administered within 1 month following the recommended interval for vaccines scheduled in the first year of life, or within 2 months following the recommended interval for vaccines scheduled later in life (see Table 1), too short, or too long after the previous dose, for each gender.

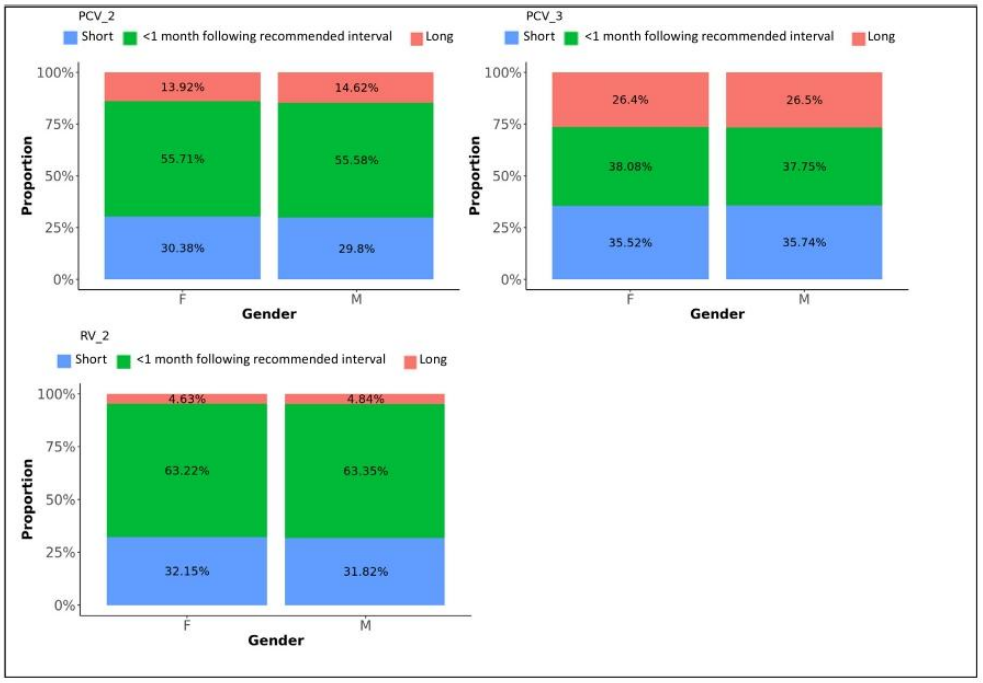


**Fig. 5** (*continued*)

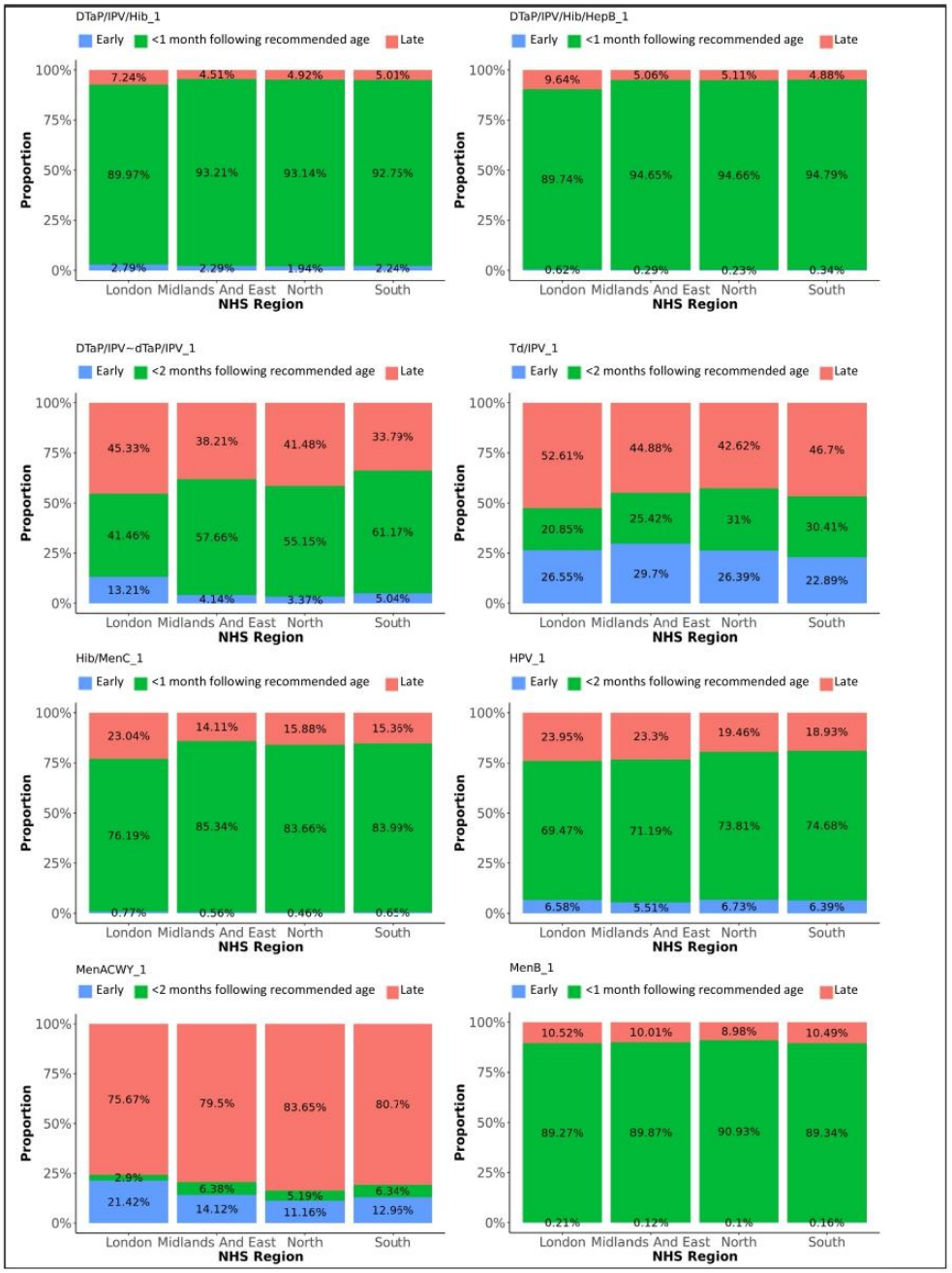


**Fig. 6.** Difference in adherence between NHS regions, for first doses. The graphs present the proportions of each vaccine's first dose administered early, within 1 month following the recommended age for vaccines scheduled in the first year of life, or within 2 months following the recommended age for vaccines scheduled later in life (see Table 1), or late, for each NHS region.

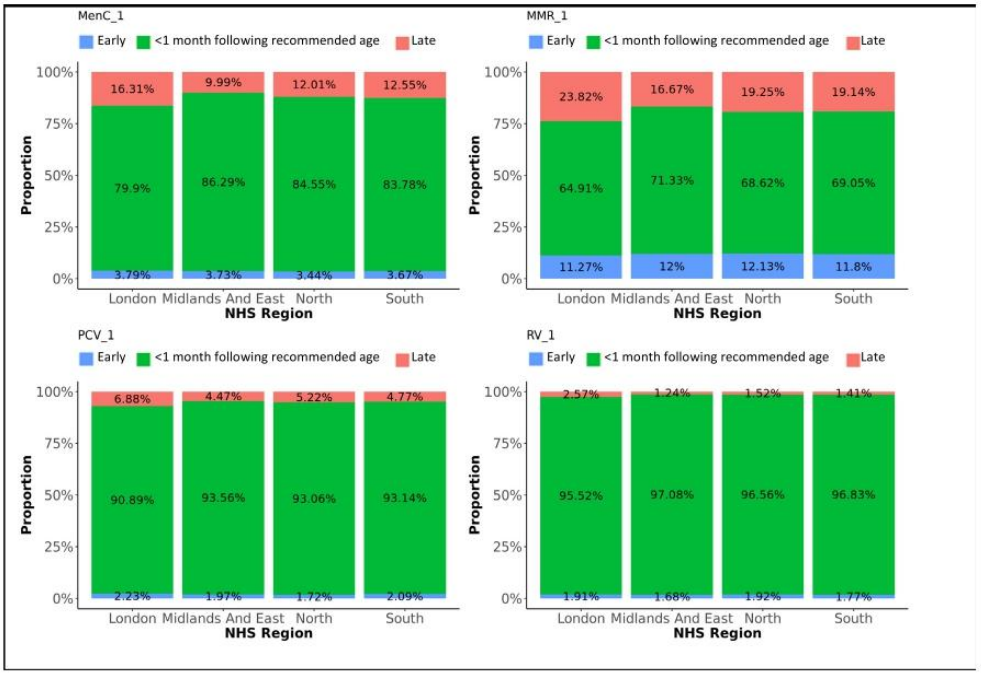


**Fig. 6** (*continued*)

efforts should involve educational, clinical, and policy interventions targeted at improving the infrastructure used for vaccine delivery, training health care professionals, and educating parents to raise awareness about the importance of timely vaccinations [3,25,50–52]. Also strengthening the relationship between the health care providers and particularly parents with several children and families with a lower educational level or lower socioeconomic status is an approach that should be considered [26,53–55].

High vaccination coverage might mask that children are suboptimally immunised and protected during some time in their childhood due to untimely vaccinations. Therefore, immunisation campaigns should aim to improve the timeliness of paediatric vaccinations, in addition to improving overall coverage, for an optimal protection against vaccine preventable diseases. We also propose developing a coefficient to adjust coverage rates accounting for poor vaccine schedule adherence or untimely vaccinations. Coverage rates are typically measured at 1 year, 2 years, and 5 years of age [56], which is between eight and 20 months after the scheduled ages for the last doses of routine paediatric vaccines. This means that discordances between real vaccinations and the immunisation schedule, and potentially long periods with lower coverage and a lack of protection, are inadequately monitored. A monitoring tool that considers the timelines of vaccinations - for instance through a build-in algorithm in the electronic health record - could also assist clinicians in following up not only the completeness of vaccine series, but also the timeliness of doses, thereby indicating potentially invalid doses that may not induce an optimal protection. Therefore, we suggest defining a measure estimating the time that the paediatric population is protected by considering effective ages of vaccination and coverage. This resulting compound measure combining coverage and adherence might provide a better indication for the protection against vaccine preventable diseases in a community.

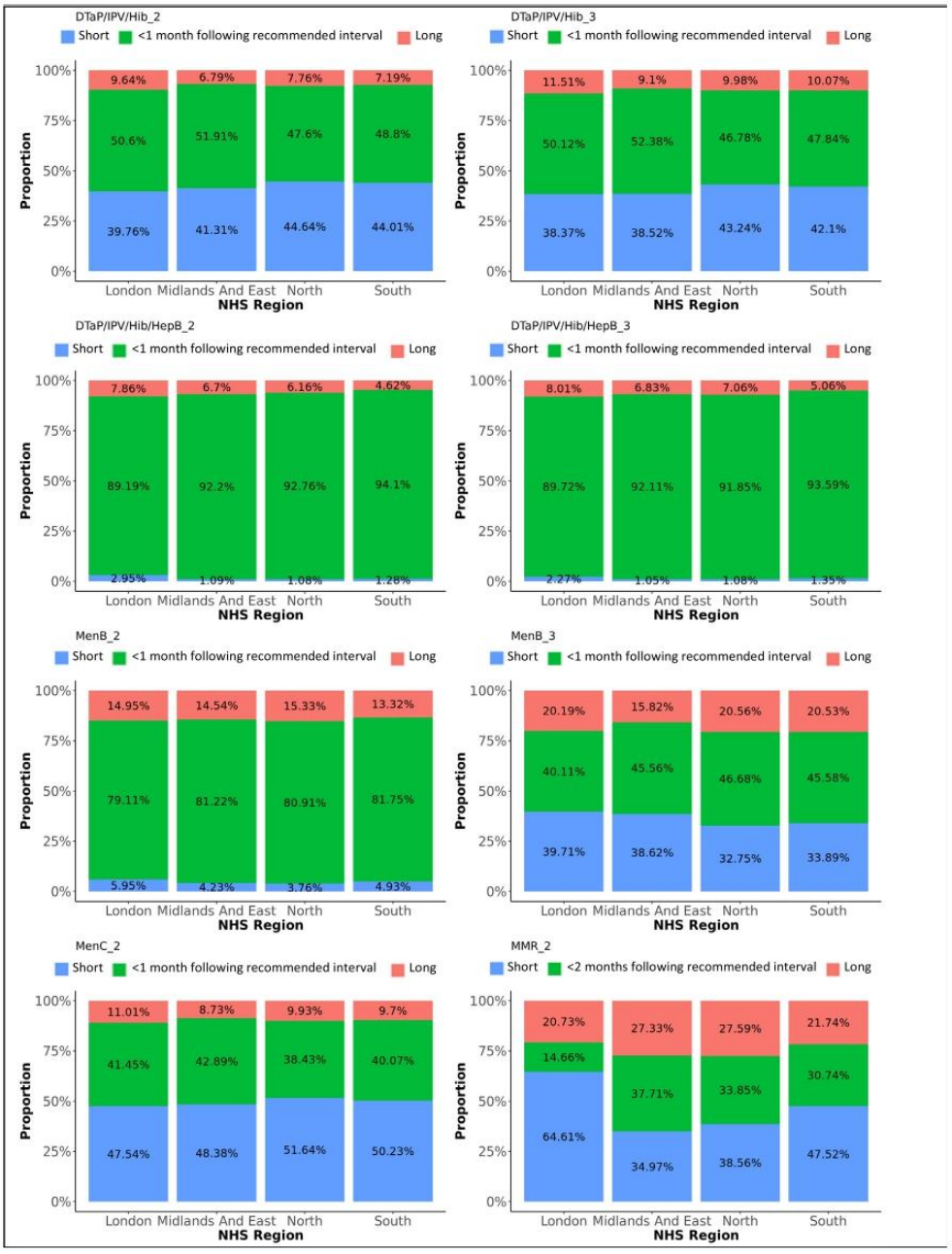


**Fig. 7.** Difference in adherence between NHS regions, for subsequent doses. The graphs present the proportions of each vaccine's subsequent dose administered within 1 month following the recommended interval for vaccines scheduled in the first year of life, or within 2 months following the recommended interval for vaccines scheduled later in life (see Table 1), too short, or too long after the previous dose, for each NHS region.

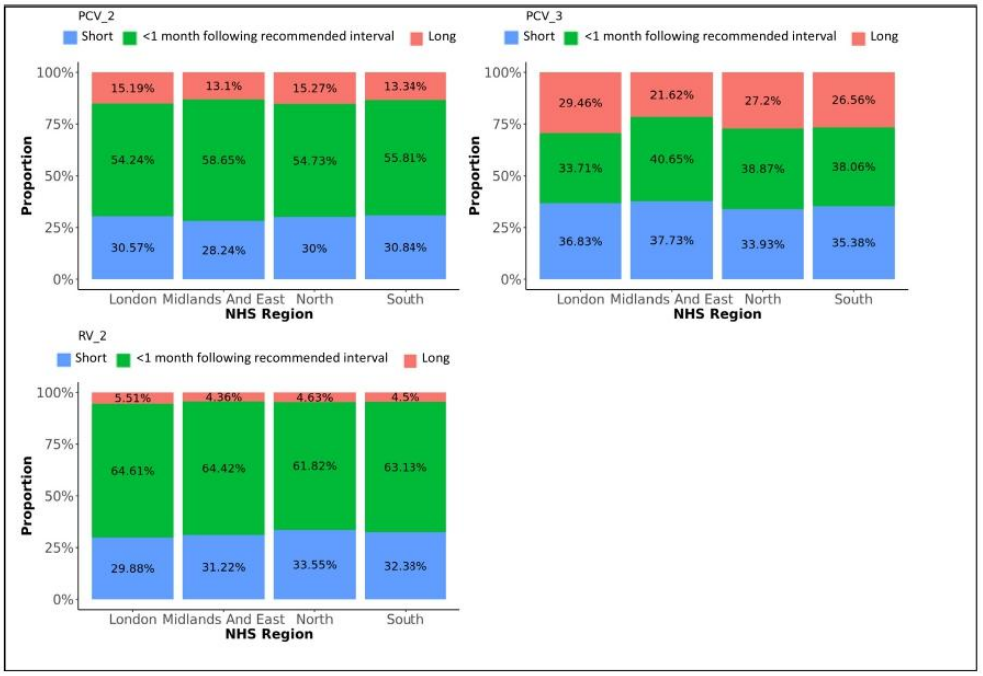


**Fig. 7** (*continued*)

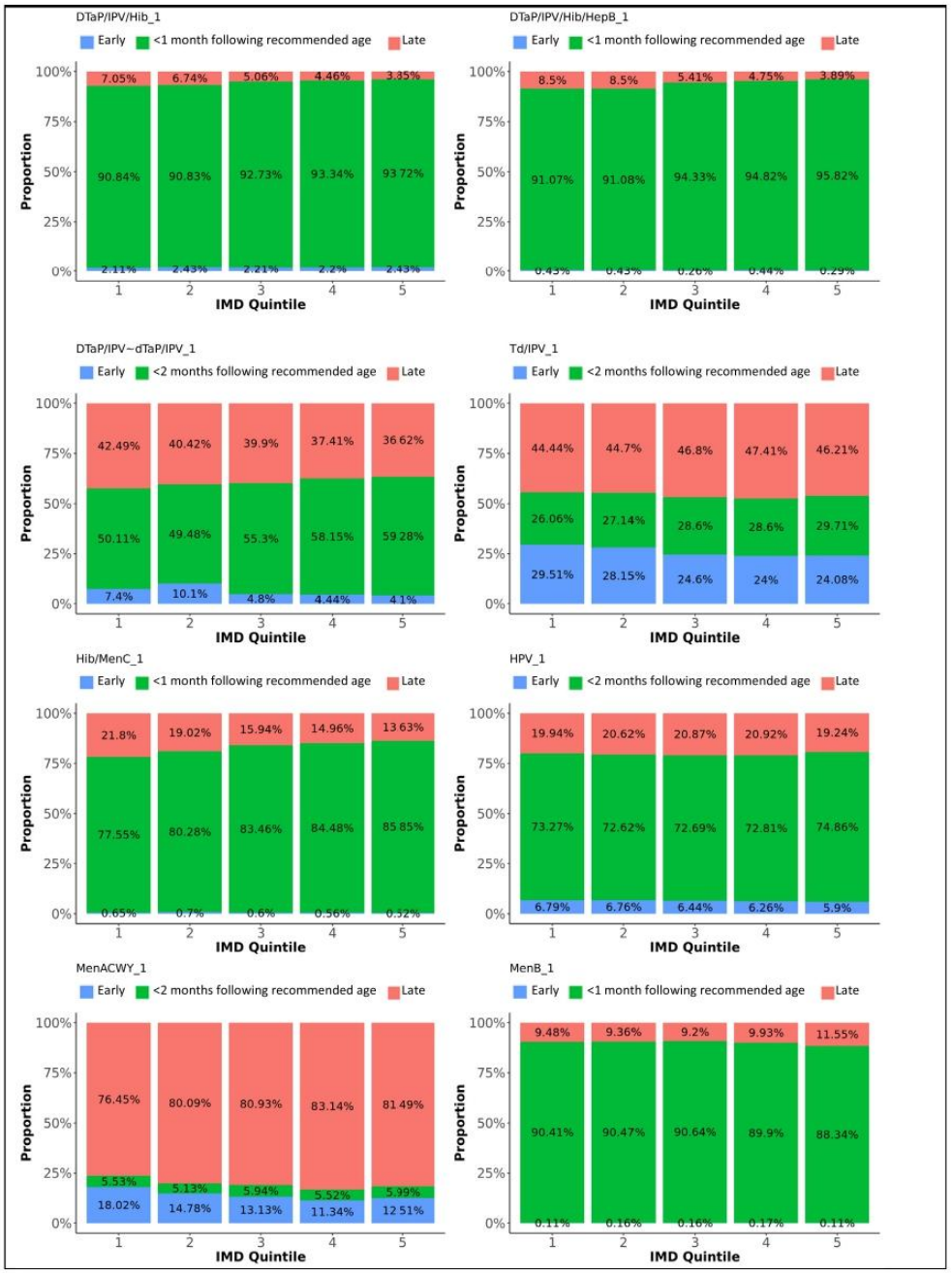


**Fig. 8.** Difference in adherence between IMD quintiles, for first doses. The graphs present the proportions of each vaccine's first dose administered early, within 1 month following the recommended age for vaccines scheduled in the first year of life, or within 2 months following the recommended age for vaccines scheduled later in life (see Table 1), or late, for each IMD quintile.

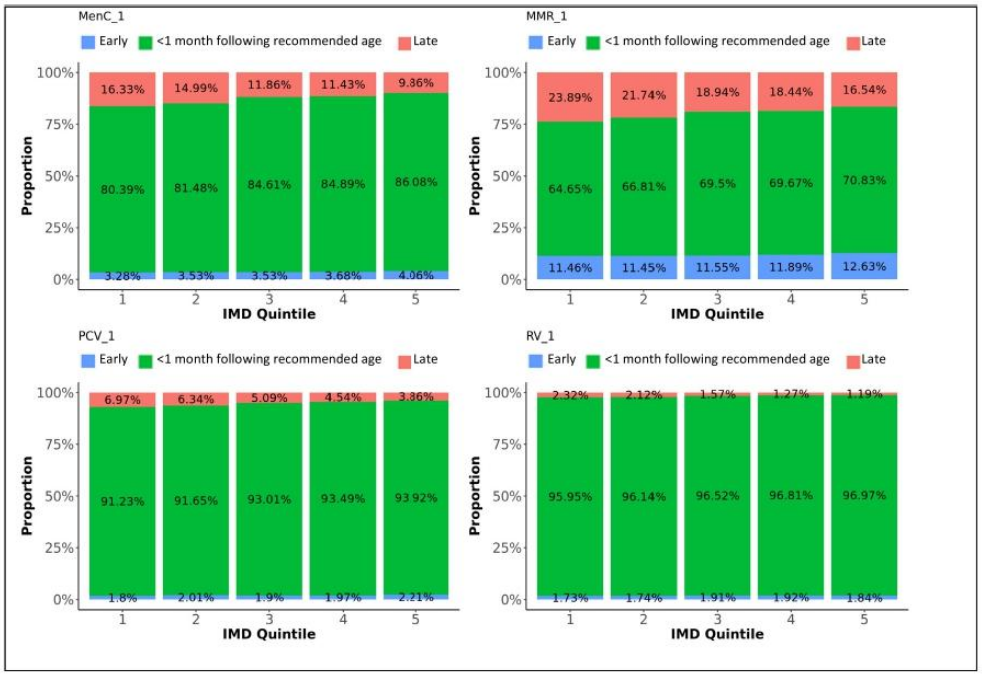


**Fig. 8** (*continued*)

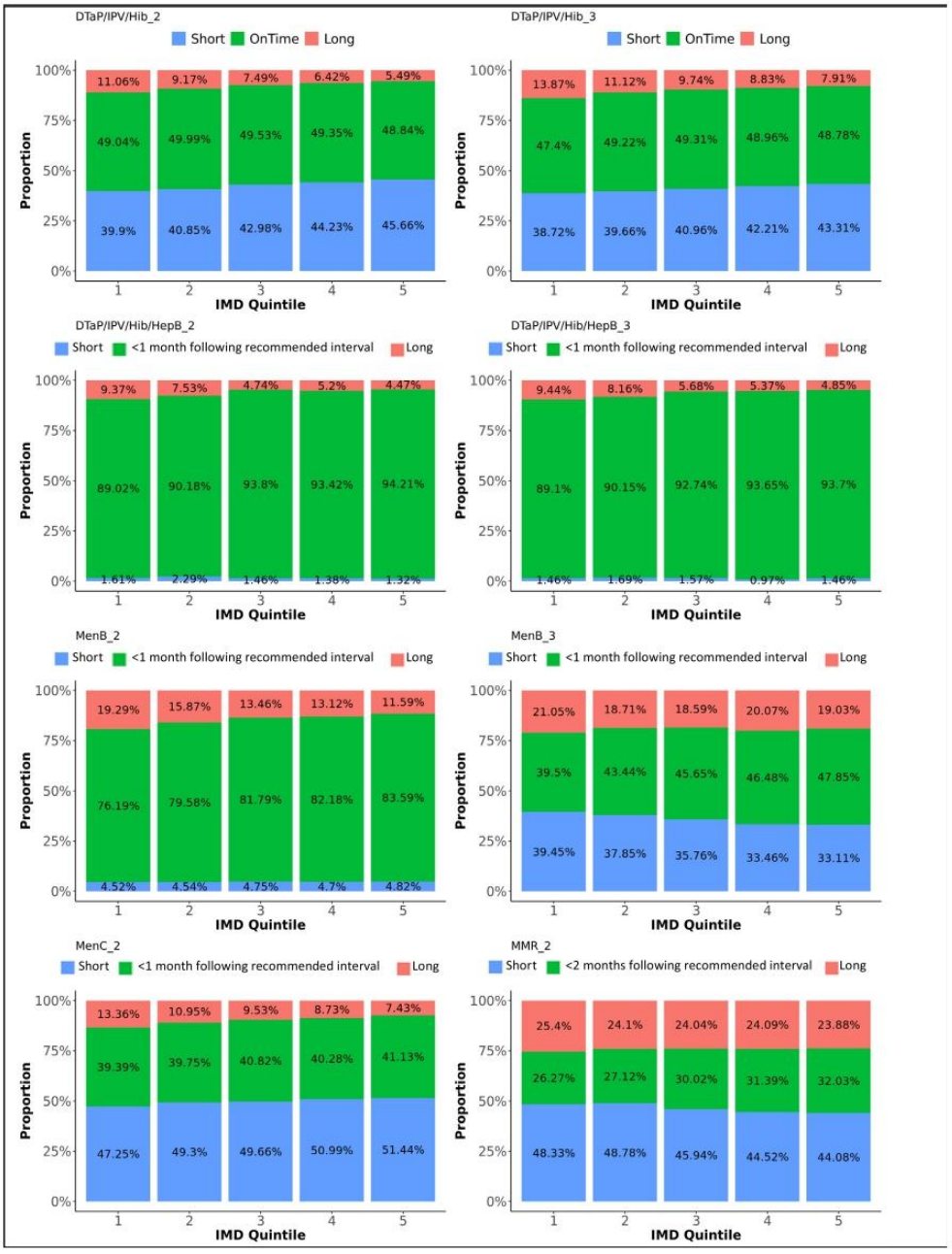


**Fig. 9.** Difference in adherence between IMD quintiles, for subsequent doses. The graphs present the proportions of each vaccine's subsequent dose administered within 1 month following the recommended interval for vaccines scheduled in the first year of life, or within 2 months following the recommended interval for vaccines scheduled later in life (see Table 1), too short, or too long after the previous dose, for each IMD quintile.

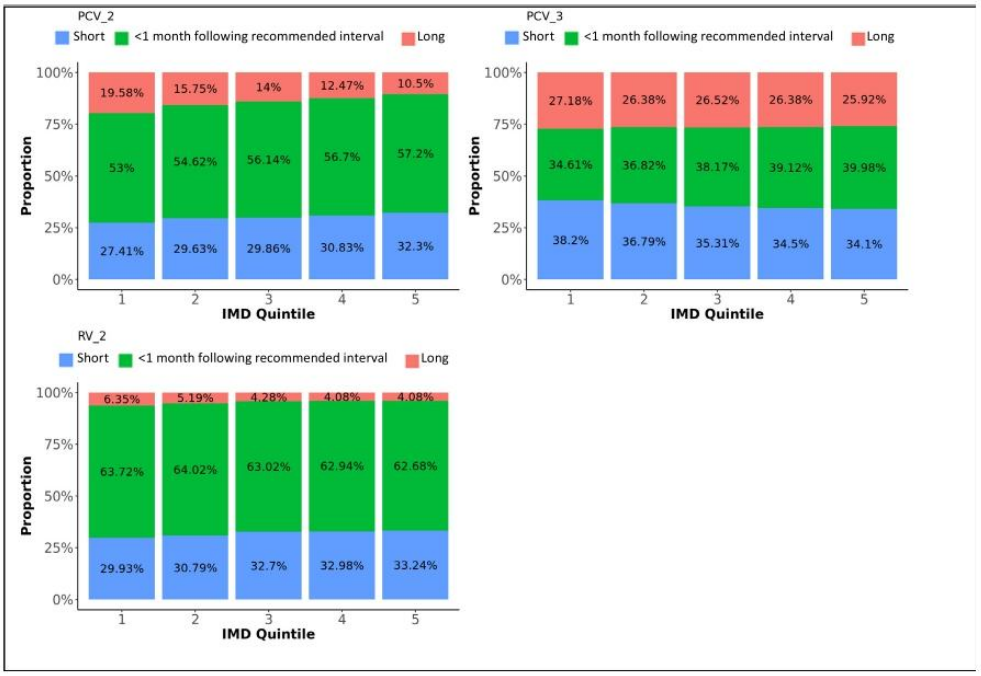


**Fig. 9** (*continued*)

**Table 3**
Odds ratios of vaccination within the defined time windows* for gender, NHS region, and IMD quintile for each of the included vaccines ($p < 0.05$).

| Vaccine and dose | Gender (comparator Female) | Region (comparator London) | | | IMD (comparator Quintile 1) | | | |
|---|---|---|---|---|---|---|---|---|
| | Male | Midland and East England | North England | South England | 2 | 3 | 4 | 5 |
| **DTaP/IPV/Hib/HepB 1** | – | 1.61 [1.42–1.84] | 1.92 [1.73–2.14] | 1.65 [1.47–1.85] | – | 1.58 [1.39–1.79] | 1.64 [1.44–1.88] | 2.01 [1.74–2.31] |
| **DTaP/IPV/Hib/HepB 2** | – | 1.19 [1.05–1.34] | 1.46 [1.32–1.63] | 1.57 [1.40–1.76] | 1.18 [1.05–1.32] | 1.8 [1.58–2.05] | 1.64 [1.45–1.87] | 1.83 [1.60–2.09] |
| **DTaP/IPV/Hib/HepB 3** | – | – | 1.24 [1.11–1.39] | 1.41 [1.24–1.59] | – | 1.51 [1.32–1.73] | 1.71 [1.48–1.97] | 1.69 [1.47–1.94] |
| **DTaP/IPV/Hib 1** | 1.03 [1.004–1.05] | 1.37 [1.32–1.43] | 1.47 [1.43–1.52] | 1.25 [1.21–1.30] | 1.04 [1.01–1.08] | 1.29 [1.25–1.34] | 1.39 [1.34–1.45] | 1.47 [1.42–1.53] |
| **DTaP/IPV/Hib 2** | – | 1.07 [1.04–1.09] | 0.89 [0.87–0.91] | 0.94 [0.92–0.96] | 1.02 [1.003–1.05] | – | – | 0.98 [0.96–0.9979] |
| **DTaP/IPV/Hib 3** | – | 1.09 [1.07–1.12] | 0.88 [0.86–0.90] | 0.91 [0.89–0.92] | 1.06 [1.04–1.09] | 1.07 [1.04–1.09] | 1.05 [1.03–1.07] | 1.05 [1.02–1.07] |
| **DTaP/IPV or dTaP/IPV** | 1.12 [1.10–1.13] | 1.79 [1.75–1.83] | 1.7 [1.67–1.74] | 2.08 [2.03–2.12] | – | 1.12 [1.10–1.15] | 1.2 [1.17–1.23] | 1.21 [1.18–1.23] |
| **Td/IPV** | – | 1.23 [1.18–1.29] | 1.69 [1.63–1.75] | 1.61 [1.55–1.67] | 1.08 [1.04–1.12] | 1.11 [1.07–1.15] | 1.09 [1.05–1.13] | 1.13 [1.09–1.17] |
| **MMR 1** | – | 1.26 [1.26–1.29] | 1.16 [1.14–1.18] | 1.12 [1.10–1.14] | 1.12 [1.09–1.14] | 1.23 [1.21–1.25] | 1.22 [1.20–1.25] | 1.29 [1.26–1.31] |
| **MMR 2** | – | 3.46 [3.36–3.57] | 2.99 [2.91–3.08] | 2.52 [2.45–2.60] | 1.14 [1.11–1.18] | 1.14 [1.11–1.17] | 1.14 [1.11–1.17] | 1.15 [1.12–1.18] |
| **PCV 1** | – | 1.31 [1.27–1.36] | 1.31 [1.27–1.35] | 1.21 [1.17–1.25] | 1.08 [1.05–1.12] | 1.26 [1.22–1.31] | 1.34 [1.29–1.38] | 1.43 [1.38–1.48] |
| **PCV 2** | – | 1.15 [1.13–1.17] | – | – | 1.07 [1.05–1.09] | 1.12 [1.10–1.14] | 1.14 [1.12–1.16] | 1.16 [1.14–1.19] |
| **PCV 3** | – | 1.29 [1.26–1.32] | 1.24 [1.21–1.26] | 1.14 [1.12–1.17] | 1.12 [1.10–1.15] | 1.16 [1.13–1.18] | 1.19 [1.16–1.22] | 1.23 [1.20–1.26] |
| **MenB 1** | – | 1.14 [1.07–1.22] | 1.23 [1.17–1.30] | 1.08 [1.02–1.14] | – | – | – | 0.81 [0.76–0.86] |
| **MenB 2** | 0.96 [0.94–0.99] | – | 1.09 [1.04–1.13] | – | 1.23 [1.17–1.29] | 1.41 [1.34–1.48] | 1.45 [1.38–1.52] | 1.6 [1.52–1.68] |
| **MenB 3** | – | 1.16 [1.06–1.27] | 1.32 [1.22–1.42] | 1.18 [1.09–1.29] | 1.22 [1.11–1.34] | 1.32 [1.21–1.44] | 1.37 [1.25–1.49] | 1.43 [1.31–1.57] |
| **MenC 1** | 1.03 [1.01–1.05] | 1.41 [1.37–1.45] | 1.33 [1.30–1.36] | 1.14 [1.11–1.17] | 1.11 [1.08–1.14] | 1.34 [1.30–1.38] | 1.34 [1.31–1.38] | 1.48 [1.44–1.52] |
| **MenC 2** | – | 1.04 [1.01–1.06] | 0.87 [0.85–0.89] | 0.92 [0.90–0.94] | – | 1.05 [1.02–1.08] | 1.03 [1.003–1.06] | 1.07 [1.04–1.10] |
| **MenACWY** | 1.15 [1.10–1.20] | 2.36 [2.12–2.63] | 1.86 [1.68–2.06] | 2.34 [2.12–2.60] | 0.88 [0.82–0.96] | – | 0.84 [0.78–0.91] | 0.89 [0.83–0.96] |
| **Hib/MenC 1** | – | 1.62 [1.57–1.66] | 1.57 [1.54–1.61] | 1.43 [1.40–1.46] | 1.23 [1.20–1.26] | 1.43 [1.39–1.47] | 1.49 [1.46–1.53] | 1.64 [1.59–1.68] |
| **Rotavirus 1** | – | 1.46 [1.35–1.59] | 1.29 [1.21–1.38] | 1.35 [1.26–1.44] | – | 1.12 [1.04–1.21] | 1.19 [1.10–1.28] | 1.23 [1.14–1.33] |
| **Rotavirus 2** | – | – | 0.89 [0.87–0.92] | 0.96 [0.93–0.98] | – | 0.96 [0.93–0.99] | 0.95 [0.92–0.98] | 0.94 [0.92–0.97] |
| **HPV 1** | 0.2 [0.16–0.24] | 1.08 [1.03–1.12] | 1.23 [1.19–1.28] | 1.27 [1.23–1.32] | – | 0.96 [0.93–0.99] | 0.96 [0.93–0.99] | 1.06 [1.02–1.09] |
| **HPV 2** | 0.32 [0.25–0.41] | 1.07 [1.03–1.12] | 1.28 [1.23–1.33] | 1.38 [1.32–1.43] | – | – | – | 1.11 [1.07–1.16] |

* Within 1 month following the recommended age or interval for vaccines scheduled in the first year of life, or within 2 months following the recommended age or interval for vaccines scheduled later in life (see Table 1).

## 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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# Manuscript 3: **Co-administration of routine paediatric vaccines in England often deviates from the immunisation schedule**

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# 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 6′257′828 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.



## 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 (see Fig. 1) [9]. Immunisation schedules are developed to assure optimal protection against vaccine preventable 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-

*Abbreviations:* DTaP/HepB/IPV/Hib, Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B, inactivated poliovirus, and *Haemophilus influenzae* type b conjugate vaccine; DTaP/IPV/Hib, Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, and *Haemophilus influenzae* type b conjugate vaccine; DTaP/IPV or dTaP/IPV, Diphtheria and tetanus toxoids and acellular pertussis adsorbed, and inactivated poliovirus vaccine; Hib/MenC, Haemophilus influenzae type b conjugate, and bivalent meningococcal conjugate vaccine; HPV, Human papillomavirus vaccine; MenACWY, Quadrivalent meningococcal conjugate vaccine; MenB, Serogroup B meningococcal vaccine; MenC, Serogroup C meningococcal vaccine; MMR, Measles, mumps, and rubella vaccine; PCV, Pneumococcal conjugate vaccine; RV, Rotavirus vaccine; Td/IPV, Tetanus and diphtheria toxoids and inactivated poliovirus vaccine; COVER, Cover of Vaccination Evaluated Rapidly; GP, General Practitioner; IMD, Index of Multiple Deprivation; IQR, Interquartile Range; OR, Odds Ratio; PHE, Public Health England; RCGP, Royal College of General Practitioners; RSC, Research and Surveillance Centre.

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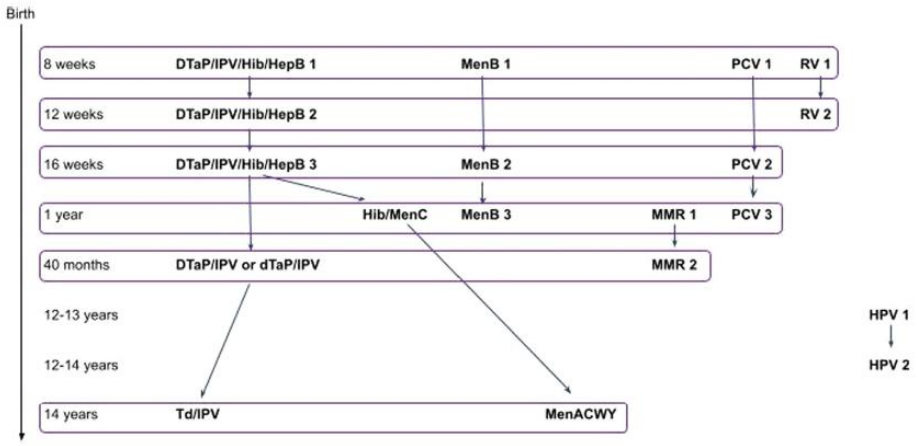


**Fig. 1.** Co-administrations in the routine paediatric immunisation schedule in 2018. [9]

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 (RCGP) 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 dTaP/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 as 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 as 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 neer 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

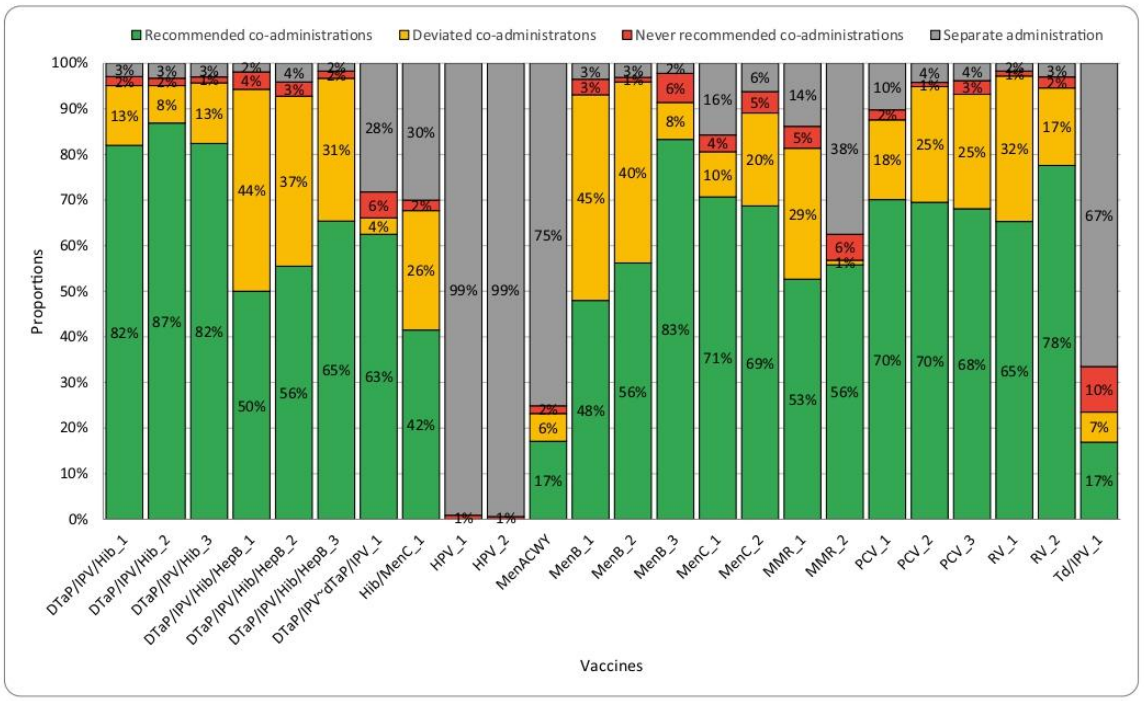


**Fig. 2.** Proportions of routine paediatric vaccine doses co-administered with at least one other vaccine according to the immunisation schedule, deviated, or off-schedule, or given separately.

**Table 1**
Vaccines most often co-administered between 2008 and 2018, by category. *Percentages indicate the proportion of each listed co-administration on the total number of vaccine co-administrations (all categories) during the study period.*

| Recommended co-administrations[1] | n | % | Scheduled ages[2] |
|---|---|---|---|
| DTaP/IPV/Hib + PCV | 274,919 | 13,9% | 8 weeks; 16 weeks |
| DTaP/IPV or dTaP/IPV + MMR | 205,362 | 10,4% | 40 months |
| DTaP/IPV/Hib + MenC | 194,083 | 9,8% | 3 months; 4 months |
| DTaP/IPV/Hib + MenC + PCV | 180,688 | 9,2% | 4 months |
| Hib/MenC + MMR + PCV | 148,218 | 7,5% | 1 year |
| MMR + PCV | 91,134 | 4,6% | 1 year |
| DTaP/IPV/Hib + MenC + RV | 89,332 | 4,5% | 3 months |
| DTaP/IPV/Hib + PCV + RV | 74,704 | 3,8% | 2 months |
| DTaP/IPV/Hib + MenB + PCV | 42,154 | 2,1% | 8 weeks; 16 weeks; 1 year |
| DTaP/IPV/Hib + RV | 40,668 | 2,1% | 8 weeks; 12 weeks |
| **Deviated co-administrations[3]** | **n** | **%** | **Scheduled ages** |
| Hib/MenC + MMR + PCV | 52,121 | 2,6% | 1 year |
| MenC + PCV | 43,965 | 2,2% | 4 months |
| Hib/MenC + MMR | 41,995 | 2,1% | 1 year |
| MMR + PCV | 35,025 | 1,8% | 1 year |
| DTaP/IPV/Hib + MenB + PCV | 29,183 | 1,5% | 8 weeks; 16 weeks; 1 year |
| DTaP/IPV/Hib + MenB + PCV + RV | 28,872 | 1,5% | 8 weeks |
| DTaP/IPV/Hib + PCV | 23,602 | 1,2% | 8 weeks; 16 weeks |
| DTaP/IPV/Hib + MenC | 21,005 | 1,1% | 3 months; 4 months |
| DTaP/IPV/Hib/HepB + MenB + PCV + RV | 14,309 | 0,7% | 8 weeks |
| DTaP/IPV/Hib + MenC + PCV | 12,509 | 0,6% | 4 months |
| **Never recommended co-administrations[4]** | **n** | **%** | **Scheduled ages[5]** |
| MMR + Td/IPV | 10,927 | 0,6% | See Fig. 1 |
| MenC + MMR + PCV | 8779 | 0,4% | See Fig. 1 |
| DTaP/IPV/Hib + MMR | 7452 | 0,4% | See Fig. 1 |
| DTaP/IPV or dTaP/IPV + PCV | 6800 | 0,3% | See Fig. 1 |
| MenC + MMR | 4922 | 0,2% | See Fig. 1 |
| DTaP/IPV or dTaP/IPV + Hib/MenC + MMR | 2834 | 0,1% | See Fig. 1 |
| DTaP/IPV/Hib + MenB + MenC + RV | 2748 | 0,1% | See Fig. 1 |
| DTaP/IPV or dTaP/IPV + Hib/MenC | 2127 | 0,1% | See Fig. 1 |
| MenB + MenC + MMR + PCV | 1630 | 0,1% | See Fig. 1 |
| HPV + Td/IPV | 1273 | 0,1% | See Fig. 1 |

[1] Vaccines co-administered exactly as recommended in the immunisation schedule.
[2] Scheduled ages for co-administering the vaccines according to the most recent immunisation schedule in the study period.
[3] Vaccine co-administrations deviating from the actual immunisations schedule (includes vaccines co-administered according to an outdated schedule, vaccines co-administered according to the immunisation schedule but not the recommended doses of these vaccines, vaccines co-administered according to an outdated schedule but with shifted doses, or co-administrations lacking at least one of the vaccines scheduled to be co-administered together.
[4] Co-administered vaccines that were never scheduled together.
[5] The individual ages for administering each of these vaccines can be found in Fig. 1 for the most recent immunisation schedule in the study period. These vaccines were at no age scheduled for co-administration.

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 paediatric vaccines are given on time and almost 20% too late [15]. These findings demonstrate that there is room to improve the timeliness of paediatric vaccinations, and that efforts aiming at this could also improve the ratio of recommended vaccine co-administrations.

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 foreseen 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 missingness, 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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# Manuscript 4: **Safety of routine childhood vaccine coadministration versus separate vaccination**

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# Safety of routine childhood vaccine coadministration versus separate vaccination

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## ABSTRACT

**Introduction** As new vaccines are developed more vaccine coadministrations vaccines are being offered to make delivery more practical for health systems and patients. We compared the safety of coadministered vaccines with separate vaccination for 20 coadministrations by considering nine types of adverse events following immunisation (AEFI).

**Methods** Real-life immunisation and adverse event data for this observational cohort study were extracted from the Oxford-Royal College of General Practitioners Research and Surveillance Centre for children registered in the database between 2008 and 2018. We applied the self-controlled case series method to calculate relative incidence ratios (RIR) for AEFI. These RIRs compare the RI of AEFI following coadministration with the RI following separate administration of the same vaccines.

**Results** We assessed 3 518 047 adverse events and included 5 993 290 vaccine doses given to 958 591 children. 17% of AEFI occurred less and 11% more frequently following coadministration than would have been expected based on the RIs following separate vaccinations, while there was no significant difference for 72% of AEFI. We found amplifying interaction effects for AEFI after five coadministrations comprising three vaccines: for fever (RIR 1.93 (95% CI 1.63 to 2.29)), rash (RIR 1.49 (95% CI 1.29 to 1.74)), gastrointestinal events (RIR 1.31 (95% CI 1.14 to 1.49)) and respiratory events (RIR 1.27 (1.17–1.38)) following DTaP/IPV/Hib+MenC+PCV; gastrointestinal events (RIR 1.65 (95% CI 1.35 to 2.02)) following DTaP/IPV/Hib+MenC+ RV; fever (RIR 1.44 (95% CI 1.09 to 1.90)) and respiratory events (RIR 1.40 (95% CI 1.25 to 1.57)) following DTaP/IPV/Hib+PCV+ RV; gastrointestinal (RIR 1.48 (95% CI 1.20 to 1.82)) and respiratory events (RIR 1.43 (95% CI 1.26 to 1.63)) following MMR+Hib/MenC+PCV; gastrointestinal events (RIR 1.68 (95% CI 1.07 to 2.64)) and general symptoms (RIR 11.83 (95% CI 1.28 to 109.01)) following MMR+MenC+PCV. Coadministration of MMR+PCV led to more fever (RIR 1.91 (95% CI 1.83 to 1.99)), neurological events (RIR 2.04 (95% CI 1.67 to 2.49)) and rash (RIR 1.06 (95% CI 1.01 to 1.11)) compared with separate administration, DTaP/IPV/Hib+MMR to more musculoskeletal events (RIR 3.56 (95% CI 1.21 to 10.50)) and MMR+MenC to more fever (RIR 1.58 (95% CI 1.37 to 1.82)). There was no indication that unscheduled coadministrations are less safe than scheduled coadministrations.

**Conclusion** Real-life RIRs of AEFI justify coadministering routine childhood vaccines according to the immunisation schedule. Further research into the severity of AEFI following coadministration is required for a complete understanding of the burden of these AEFI.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vaccine coadministration may lead to interactions between individual products and alter health outcomes. Information about the safety of real-life vaccine coadministrations versus separate vaccinations is scarce and a potential source for vaccine hesitancy.

### WHAT THIS STUDY ADDS

⇒ Coadministering two vaccines decreases the relative incidence of severaladverse events following immunisation (AEFI) compared with separately administering the respective vaccines, while adding a third vaccine can lead to a higher than expected relative incidence of AEFI.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Real-life relative incidence ratios of AEFI justify the coadministration of routine childhood vaccines as recommended in immunisation schedules. Nevertheless, health systems should run enhanced surveillance for a comprehensive monitoring of the burden of AEFI following vaccine coadministration.

## INTRODUCTION

As new vaccines are developed to protect against a growing number of vaccine-preventable diseases, vaccine coadministrations will gain importance to make immunising more practicable for health systems and patients globally. Vaccine coadministration practices cost-effectively facilitate the introduction of new vaccines into immunisation

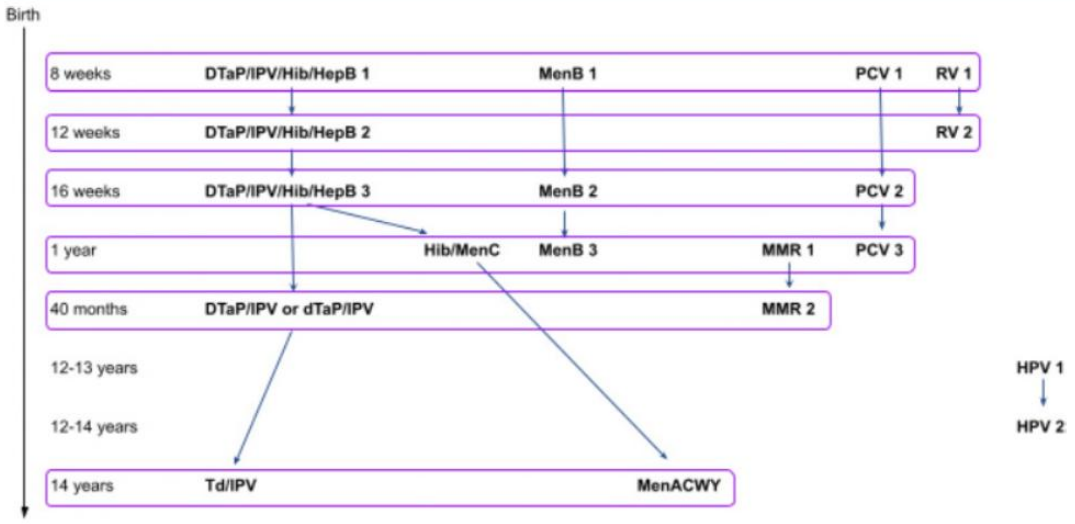


**Figure 1** Coadministrations in the routine paediatric immunisation schedule NHS 2018.[6] NHS, National Health Service.

programmes and improve coverage rates.[1–5] According to the National Health Service and Public Health England's immunisation schedule for 2018, between two and four vaccines were scheduled for coadministration at six time points between birth and 14 years, adding up to 17 vaccines (first and subsequent doses) for 16 different antigens (figure 1).[6] However, coadministering vaccines may lead to interactions between individual products and alter their health outcomes.[7–9] Therefore, insights in the effectiveness and safety profiles of vaccine coadministration are essential to inform vaccination regimens.[9] Furthermore, safety information can overcome uncertainties about the health outcomes of coadministered vaccines, which is a driver for vaccine hesitancy in parents.[10 11]

All recommended paediatric routine immunisations can be coadministered and there are no recommendations against coadministration, unless reported in the Summary of Product Characteristics.[12 13] Coadministration is explicitly endorsed by the WHO for some vaccines, while it does not mean that the vaccines without such endorsement cannot be coadministered.[14] Furthermore, studying the safety of paediatric immunisation schedules, for example, whether health outcomes differ for children who receive fewer immunisations per physician visit, is recommended by the Institute of Medicine.[15] A recent literature review showed that the safety of vaccine coadministrations versus separate vaccinations is mostly assessed in prelicensure clinical trials, while data on the extent and impact of vaccine coadministrations in real life postlicensure are scarce.[16] To fill this gap, we compared the safety of coadministering vaccines versus the safety of separately administering the same vaccines for 20 coadministrations including real life both schedule and off-schedule coadministrations

## METHODS

The study population and data collection methods were previously described in detail.[17 18] In brief, data for our observational cohort study were extracted from the Oxford-Royal College of General Practitioners Research and Surveillance Centre, a national, electronic primary healthcare medical record database, representative of the English population.[19 20] 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 scheduled age for the first dose of a vaccine. The extracted data were pseudonymised and managed according to privacy and data protection regulations. Neither patients nor the public were involved in this study.

We included paediatric vaccines that were given in the 10 most frequent vaccine coadministrations according to the immunisation schedule and the ten most frequent unscheduled coadministrations (vaccines that were never scheduled together) between 2008 and 2018: DTaP/IPV/Hib, DTaP/IPV, dTaP/IPV, Td/IPV, MMR, PCV, MenB, MenC, Hib/MenC, RV and HPV.[6 18 21–28] The selected vaccine coadministrations are presented in table 1.[18] An overview of the changes in the immunisation schedule during the study period has been documented before.[17] We collected the vaccination types and dates for each vaccination. Records with a missing patient-ID, vaccination type or date were excluded. We selected 33 potential adverse events following immunisation (AEFI) based on their occurrence in previous studies[16] and grouped these in 9 types of AEFI as listed in table 2. All event dates during the study period for each of the included children were collected.

**Table 1** Number of scheduled and off-schedule vaccine coadministrations[18]

| Coadministrations according to schedule* | n | % | Off-schedule coadministrations | n | % |
|---|---|---|---|---|---|
| DTaP/IPV/Hib+PCV | 274 919 | 13.9 | MMR+Td/IPV | 10 927 | 0.6 |
| DTaP/IPV or dTaP/IPV+MMR | 205 362 | 10.4 | MenC+MMR + PCV | 8779 | 0.4 |
| DTaP/IPV/Hib+MenC | 194 083 | 9.8 | DTaP/IPV/Hib+MMR | 7452 | 0.4 |
| DTaP/IPV/Hib+MenC+PCV | 180 688 | 9.2 | DTaP/IPV or dTaP/IPV+PCV | 6800 | 0.3 |
| Hib/MenC+MMR+PCV | 148 218 | 7.5 | MenC+MMR | 4922 | 0.2 |
| MMR+PCV | 91 134 | 4.6 | DTaP/IPV or dTaP/IPV+Hib/MenC+MMR | 2834 | 0.1 |
| DTaP/IPV/Hib+MenC+RV | 89 332 | 4.5 | DTaP/IPV/Hib+MenB + MenC + RV | 2748 | 0.1 |
| DTaP/IPV/Hib+PCV+RV | 74 704 | 3.8 | DTaP/IPV or dTaP/IPV+Hib/MenC | 2127 | 0.1 |
| DTaP/IPV/Hib+MenB+PCV | 42 154 | 2.1 | MenB+MenC + MMR + PCV | 1630 | 0.1 |
| DTaP/IPV/Hib+RV | 40 668 | 2.1 | HPV+Td/IPV | 1273 | 0.1 |
| Total | 1 341 262 | 67.8 | Total | 49 492 | 2.5 |

*Vaccine coadministrations given according to the immunisation schedule valid at the moment of vaccination.

We used the self-controlled case series (SCCS) method to compare the relative incidences (RI) of each type of AEFI after vaccine coadministration with their RI after separate administrations of the same vaccines. The RI compares the incidence of events in a risk period with the incidence in a control period for the same individual. The risk period was defined as 42 days postvaccination. Events in overlapping risk periods were allocated to the most recent exposure. The unexposed period encompassed the remaining time that children were registered in the database during the study period while between 0 and 18 years of age, whereby the observation period was partitioned by ages.

The SCCS model estimates the RI of an AEFI for each vaccine in absence of other vaccines, corresponding to a separate vaccine administration. These RIs are estimated by a fitted SCCS conditional Poisson model using the SCCS method.[29 30] When estimating the RI as a dependent variable, the regression model includes the independent variables: age effects; exposure effects of each of the separate vaccines; exposure effects of any vaccines coadministered. The latter covariate is thus an interaction term for the effect of coadministration on the individual vaccines' RIs. This term can be interpreted as an RI ratio (RIR) ($RIR_{interaction}$) because it corresponds to the ratio of the RI in the coadministration group ($RI_{coadministered}$) compared with the RI in the designated reference group with separate vaccinations (eg, $RI_{vaccine\ a}$, $RI_{vaccine\ b}$).[31] The factors relate as follows:

$$RIR_{interaction} = RI_{coadministered} / (RI_{vaccine\ a} \times RI_{vaccine\ b})$$

An interaction term significantly less than 1 ($p<0.05$) indicates an inhibitory interaction effect as the $RI_{coadministered}$ will be lower than expected based on the RIs of the separately administered vaccines. An interaction term significantly greater than 1 ($p<0.05$) indicates an amplifying interaction effect. Vaccination ages were included as a vector in the SCCS model to stratify the analyses and account for age-related differences in incidences. These analyses were performed in R[32] using the SCCS package.[33]

## RESULTS

A total of 5 993 290 vaccine doses delivering 13 920 730 antigen exposures to 958 591 children met our inclusion criteria for analysis. This study population was representative for the entire population in the database.[17] Twenty per cent of the included vaccines were given separately, while 80% were coadministered: 37% were coadministrations of two, 34% were coadministrations of three and 8% were c-administrations of four vaccines. The patterns of coadministration for each vaccine are shown in figure 2. Our study included 3 518 047 adverse events, which are categorised and quantified in table 2. The numbers of adverse events in the control and risk periods, which were included in the SCCS analysis, are listed in table 3.

### Coadministrations of two vaccines

Table 4 presents the RIRs of the adverse events analysed following vaccine coadministrations. The RIs of adverse events following coadministration of DTaP/IPV/Hib+PCV, DTaP/IPV or dTaP/IPV+Hib/MenC, DTaP/IPV or dTaP/IPV+MMR, DTaP/IPV or dTaP/IPV+PCV, MMR+Td/IPV or Td/IPV+HPV were not increased as compared with the separate administration of these vaccines. The RIs of respirato–ry events were lower ($RIR \leq 1$, $p<0.05$) than expected based on the separate immunisations after all coadministrations of two vaccines except Td/IPV+HPV. We also found lower RIs of gastrointestinal events after seven, and less local events and rash after each three coadministrations of two vaccines.

While the coadministration of MMR+PCV had an inhibitory interaction effect on gastrointestinal events, local symptoms and respiratory events, it led to a higher RI of fever (RIR 1.91, 95% CI 1.83 to 1.99), neurological events (RIR 2.04, 95% CI 1.67 to 2.49)—particularly convulsions—and rash (RIR 1.06, 95% CI 1.01 to 1.11). Also coadministration of DTaP/IPV/Hib+MMR led to a higher RI of musculoskeletal events (RIR 3.56, 95% CI 1.21 to 10.50) and MMR+MenC to a higher RI of fever (RIR 1.58, 95% CI 1.37 to 1.82).

**Table 2** Frequency of adverse events included in the study

| Type | n | % | Events | n | % |
|---|---|---|---|---|---|
| Fever | 446 223 | 12.68 | Fever symptoms | 268 921 | 7.64 |
| | | | High fever (>39.5°C) | 5334 | 0.15 |
| | | | Mild fever (≤38.5°C) | 139 397 | 3.96 |
| | | | Moderate fever (38.6°C–39.5°C) | 32 571 | 0.93 |
| Gastrointestinal | 432 509 | 12.29 | Diarrhoea | 218 436 | 6.21 |
| | | | Loss of appetite | 9520 | 0.27 |
| | | | Nausea | 23 177 | 0.66 |
| | | | Vomiting | 181 376 | 5.16 |
| General symptoms | 245 240 | 6.97 | Drowsiness | 771 | 0.02 |
| | | | Fatigue | 41 285 | 1.17 |
| | | | Headache | 153 319 | 4.6 |
| | | | Malaise | 45 383 | 1.29 |
| | | | O/E—irritable | 4482 | 0.13 |
| Local symptoms | 259 | 0.01 | Local erythema | 259 | 0.01 |
| Musculoskeletal | 136 835 | 3.89 | Myalgia | 134 940 | 3.84 |
| | | | Postimmunisation arthropathy | 1895 | 0.05 |
| Neurological | 32 363 | 0.92 | Bell's palsy | 1807 | 0.05 |
| | | | Convulsion/febrile convulsion | 27 688 | 0.79 |
| | | | Guillain-Barre syndrome | 113 | 0.00 |
| | | | Tremor | 2755 | 0.08 |
| Rash | 511 090 | 14.53 | Rash | 511 090 | 14.53 |
| Respiratory/miscellaneous | 1 679 864 | 47.75 | Acute conjunctivitis | 311 701 | 8.86 |
| | | | Acute coryza | 55 489 | 1.58 |
| | | | Cough | 841 733 | 23.93 |
| | | | Epistaxis | 59 632 | 1.70 |
| | | | Hoarse | 4120 | 0.12 |
| | | | Nasal airway obstruction | 54 162 | 1.54 |
| | | | Rhinorrhoea | 14 579 | 0.41 |
| | | | Sore mouth/throat pain | 219 808 | 6.25 |
| | | | Wheezing | 118 640 | 3.37 |
| Sensitivity/anaphylaxis | 33 664 | 0.96 | Adverse drug reaction/vaccine allergy | 29 217 | 0.83 |
| | | | Drug-induced anaphylaxis | 1058 | 0.03 |
| | | | Facial swelling | 3389 | 0.10 |
| Total | 3 518 047 | 100% | Total | 3 518 047 | 100.00 |

Fever and neurological events occurred less frequently (RI<1) after the vaccination of either separate or coadministration of DTaP/IPV/Hib+MenC, compared with the control periods. We observed the same for fever following DTaP/IPV/Hib+RV. However, the RIRs of these AEFI after coadministration indicated an amplifying interaction effect compared with separate vaccinations (RIR>1, p<0.05), although this effect did not raise the resulting RI's following coadministration above 1. Thus, these AEFIs remained less frequent than in the control periods.

### Coadministrations of three vaccines

While the coadministration of DTaP/IPV/Hib+PCV had an inhibitory interaction effect on fever, gastrointestinal events, rash and respiratory events compared with these vaccines' separate administrations, adding a third vaccine was associated with an RIR>1 (p<0.05) for these events in the coadministration of, DTaP/IPV/Hib+MenC + PCV (RIR 1.93, 95% CI 1.63 to 2.29; RIR 1.31, 95% CI 1.14 to 1.49; RIR 1.49, 95% CI 1.29 to 1.74; RIR 1.27, 95% CI 1.17 to 1.38). As a result, the RIs of these AEFI were higher than what would have been expected based on the RIs of these vaccines' separate administrations—particularly for diarrhoea, acute conjunctivitis and cough. Similarly, despite the inhibitory effect on gastrointestinal and respiratory events of DTaP/IPV/Hib+PCV, DTaP/IPV/Hib+MenC and DTaP/IPV/Hib+RV, the RI of gastrointestinal events—particularly vomiting—was higher after

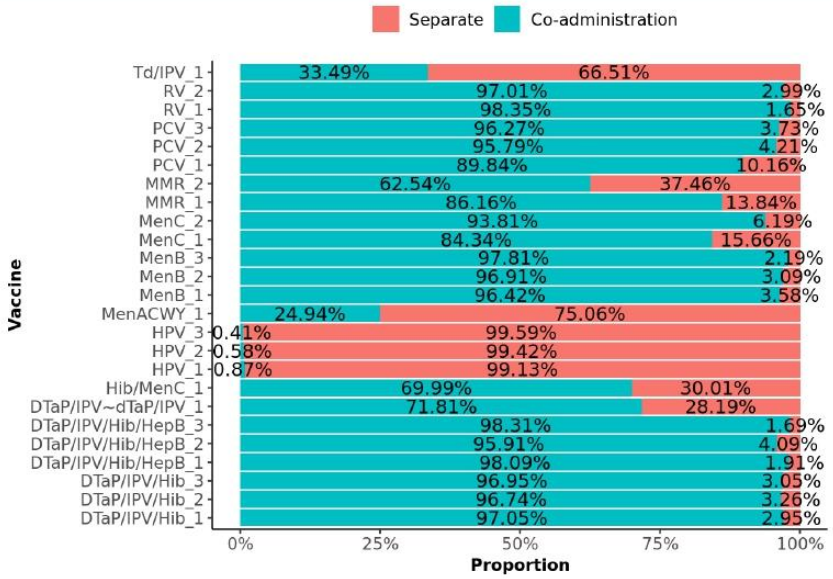


**Figure 2** Proportions of routine paediatric vaccines coadministered.

DTaP/IPV/Hib+MenC+RV (RIR 1.65, 95% CI 1.35 to 2.02) and the RI of respiratory events—articularly acute conjunctivitis, cough and wheezing—was higher after DTaP/IPV/Hib+PCV+RV (RIR 1.40, 95% CI 1.25 to 1.57). The latter also resulted in more fever (RIR 1.44; 95% CI 1.09 to 1.90). For the other AEFI included in this study, there was an inhibitory or no significant effect on the RIs following coadministration of DTaP/IPV/Hib+MenB+PCV, DTaP/IPV/Hib+MenC+PCV, DTaP/IPV/Hib+MenC+RV and DTaP/IPV/Hib+PCV+RV (see table 4).

Coadministering MMR+MenC and MMR+PCV had an inhibitory interaction effect on gastrointestinal and respiratory events, as well as local symptoms (erythema) for the latter, compared with separate vaccine administrations, while coadministering MMR+MenC+PCV was associated with an RIR>1 ($p<0.05$) for gastrointestinal events (RIR 1.68, 95% CI 1.07 to 2.64)—particularly vomiting—and general symptoms (RIR 11.83, 95% CI 1.28 to 109.01). Also the RIRs for gastrointestinal (RIR 1.48, 95% CI 1.20 to 1.82)—particularly diarrhoea and vomiting—and respiratory events (RIR 1.43, 95% CI 1.26 to 1.63)—acute conjunctivitis and cough—were >1 ($p<0.05$) after MMR+Hib/MenC+PCV. There was no or an inhibitory interaction effect of coadministering MMR+Hib/MenC+PCV, MMR+MenC + PCV, or DTaP/IPV or dTaPIPV+MMR+Hib/MenC on the other events included in this study (see table 4).

### Coadministration of four vaccines

Adding a fourth vaccine did not significantly alter the amplifying effects observed when coadministering three vaccines for any of the investigated AEFI.

## DISCUSSION

The RIs following vaccine coadministration for most of the analysed AEFI (72%) were not significantly different from what would have been expected based on the RIs following separate administration of the respective vaccines, while we found an amplifying effect following coadministration for 11% and an inhibitory effect for 17% of AEFI studied. Although studies comparing the safety of coadministration with separate vaccination are rare, an earlier literature review found increased AEFI following coadministration in 16% of studies, less AEFI following coadministration in 10% of studies, while the majority of studies found no statistically significant differences in the incidence of any AEFI following coadministration compared with separate administration of the same vaccines.[16] We found more differences in the incidence between coadministration and separate administration of vaccines, likely because our study was designed specifically to detect such differences while the majority of reviewed studies were clinical trials not designed to demonstrate statistically significant safety differences.[16]

Half of the 20 investigated vaccine coadministrations led to a higher reactogenicity for at least one AEFI. We found amplifying interaction effects for five out of seven investigated coadministrations of three vaccines. Such an increased reactogenicity is often reported when coadministering three vaccines. DTaP/IPV/Hib+MenC+PCV led to more fever, rash, gastrointestinal and respiratory events compared with the separate administration of these vaccines. Other studies also reported fever, local and general symptoms, and gastrointestinal events following this coadministration.[34 35] We found increased gastrointestinal events (vomiting) after DTaP/

**Table 3** Numbers of adverse events in the risk and control periods, included in the self-controlled case series analysis

| Adverse events | Period | Vaccines | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | DTaP/IPV or dTaP/IPV | | DTaP/IPV/Hib | | Hib/MenC | | HPV | | MenB | | MenC | | MMR | | PCV | | RV | | Td/IPV | |
| | | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| Fever | Risk | 4620 | 1.0 | 3089 | 0.7 | 12 733 | 2.9 | 255 | 0.1 | 1 728 | 0.4 | 3 684 | 0.8 | 13 751 | 3.1 | 3 982 | 0.9 | 2 227 | 0.5 | 379 | 0.1 |
| | Control | 441 603 | 99.0 | 443 134 | 99.3 | 433 490 | 97.1 | 445 968 | 99.9 | 444 495 | 99.6 | 442 539 | 99.2 | 432 508 | 96.9 | 442 241 | 99.1 | 443 996 | 99.5 | 445 844 | 99.9 |
| Gastrointestinal | Risk | 2206 | 0.5 | 10 549 | 2.4 | 9969 | 2.3 | 520 | 0.1 | 3 311 | 0.8 | 11 191 | 2.6 | 10 662 | 2.5 | 13 062 | 3.0 | 5 684 | 1.3 | 634 | 0.1 |
| | Control | 430 303 | 9.5 | 429 198 | 97.6 | 422 540 | 97.7 | 431 989 | 99.9 | 429 198 | 99.2 | 421 318 | 97.4 | 421 847 | 97.5 | 419 447 | 97.0 | 426 825 | 98.7 | 431 875 | 99.9 |
| General symptoms | Risk | 557 | 0.2 | 829 | 0.3 | 1 016 | 0.4 | 1 157 | 0.5 | 280 | 0.1 | 846 | 0.3 | 1 249 | 0.5 | 1 072 | 0.4 | 439 | 0.2 | 1 115 | 0.5 |
| | Control | 244 683 | 99.8 | 244 411 | 99.7 | 244 224 | 99.6 | 244 083 | 99.5 | 244 960 | 99.9 | 244 394 | 99.7 | 243 991 | 99.5 | 244 168 | 99.6 | 244 801 | 99.8 | 244 125 | 99.5 |
| Local symptoms | Risk | 54 | 20.8 | 17 | 6.6 | 31 | 12.0 | 1 | 0.4 | 9 | 3.5 | 22 | 8.5 | 42 | 16.2 | 31 | 12.0 | 8 | 3.1 | 5 | 1.9 |
| | Control | 205 | 79.2 | 242 | 93.4 | 228 | 88.0 | 258 | 99.6 | 250 | 96.5 | 237 | 91.5 | 217 | 84.8 | 228 | 88.0 | 251 | 96.9 | 254 | 98.1 |
| Musculoskeletal | Risk | 473 | 0.3 | 54 | 0.0 | 255 | 0.2 | 527 | 0.4 | 35 | 0.0 | 81 | 0.1 | 330 | 0.2 | 76 | 0.1 | 36 | 0.0 | 526 | 0.4 |
| | Control | 136 362 | 99.7 | 136 781 | 100.0 | 136 580 | 99.8 | 136 308 | 99.6 | 136 800 | 100.0 | 136 754 | 99.9 | 136 505 | 99.8 | 136 759 | 99.9 | 136 799 | 100.0 | 136 309 | 99.6 |
| Neurological | Risk | 187 | 0.6 | 168 | 0.5 | 860 | 2.7 | 43 | 0.1 | 63 | 0.2 | 205 | 0.6 | 1 012 | 3.1 | 212 | 0.7 | 85 | 0.3 | 36 | 0.1 |
| | Control | 32 176 | 99.4 | 32 195 | 99.5 | 31 503 | 97.3 | 32 320 | 99.9 | 32 300 | 99.8 | 32 158 | 99.4 | 31 351 | 96.9 | 32 151 | 99.3 | 32 278 | 99.7 | 32 327 | 99.9 |
| Rash | Risk | 3567 | 0.7 | 6 353 | 1.2 | 11 709 | 2.3 | 630 | 0.1 | 2490 | 0.5 | 8 010 | 1.6 | 13 622 | 2.7 | 8060 | 1.6 | 3 934 | 0.8 | 712 | 0.1 |
| | Control | 507 523 | 99.3 | 504 737 | 98.8 | 499 381 | 97.7 | 510 460 | 99.9 | 508 600 | 99.5 | 503 080 | 98.4 | 497 468 | 97.3 | 503 030 | 98.4 | 507 156 | 99.2 | 510 378 | 99.9 |
| Respiratory / Misc | Risk | 11 527 | 0.7 | 25 833 | 1.5 | 28 214 | 1.7 | 2 533 | 9.2 | 8 707 | 0.5 | 29 191 | 1.7 | 31 642 | 1.9 | 32 917 | 2.0 | 14 267 | 0.8 | 2 506 | 0.1 |
| | Control | 1 668 337 | 99.3 | 1 654 031 | 98.5 | 1 651 650 | 98.3 | 1 677 331 | 99.8 | 1 671 157 | 99.5 | 1 650 763 | 98.3 | 1 648 222 | 98.1 | 1 646 947 | 98.0 | 1 665 597 | 99.2 | 1 677 358 | 99.9 |
| Sensitivity / Anaphylaxis | Risk | 353 | 1.0 | 154 | 0.5 | 477 | 1.4 | 118 | 0.4 | 72 | 0.2 | 201 | 0.6 | 505 | 1.5 | 194 | 0.6 | 107 | 0.3 | 119 | 0.4 |
| | Control | 33 311 | 99.0 | 33 510 | 99.5 | 33 187 | 98.6 | 33 546 | 99.6 | 33 592 | 99.8 | 33 463 | 99.4 | 33 159 | 98.5 | 33 470 | 99.4 | 33 557 | 99.7 | 33 545 | 99.6 |

**Table 4** (A) Relative incidence ratios (RIR) and interaction effects of the adverse events for all recommended coadministrations studied. (B) RIR and interaction effects of the adverse events for all never recommended coadministrations studied

| Vaccines coadministered | No of vaccines | RIR; (95% CI); p value; interaction | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Fever | Gastrointestinal | General symptoms | Local symptoms | Musculoskeletal | Neurological | Rash | Respiratory/ misc | Sensitivity/ anaphylaxis |
| (A) RIR and interaction effects of the adverse events for all recommended coadministrations studied | | | | | | | | | | |
| DTaP/IPV or dTaP/IPV+MMR | 2 | 0.76 | 0.76 | 1.24 | 0.42 | 1.09 | 1.12 | 0.78 | 0.87 | 1.00 |
| | | (0.70 to 0.82) | (0.68 to 0.84) | (0.85 to 1.80) | (0.09 to 1.90) | (0.71 to 1.68) | (0.68 to 1.84) | (0.71 to 0.87) | (0.83 to 0.92) | (0.63 to 1.59) |
| | | $6.57\times10^{-11}$ | $7.34\times10^{-7}$ | 0.258 | 0.26 | 0.686 | 0.66 | $2.77\times10^{-6}$ | $9.85\times10^{-7}$ | 0.988 |
| | | Inhibitory | Inhibitory | Non-significant | Non-significant | Non-significant | Non-significant | Inhibitory | Inhibitory | Non-significant |
| DTaP/IPV/Hib+MenB+PCV | 3 | 1.25 | 1.29 | 942.2 | 350.8 | $8.38\times10^{+8}$ | $5.31\times10^{+4}$ | 0.95 | 1.14 | 0.22 |
| | | (0.80 to 1.95) | (0.81 to 2.06) | ($1.65\times10^{-98}$ to $5.39\times10^{+103}$) | (0.00-inf) | (0.00-inf) | ($6.13\times10^{-222}$ to $40.60\times10^{+234}$) | (0.58 to 1.54) | (0.86 to 1.50) | (0.01 to 4.19) |
| | | 0.333 | 0.282 | 0.954 | 1 | 0.973 | 0.967 | 0.821 | 0.359 | 0.313 |
| | | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant |
| DTaP/IPV/Hib+MenC | 2 | 1.51 | 0.74 | 0.78 | 0.33 | 0.91 | 2.48 | 0.94 | 0.8 | 1.29 |
| | | (1.41 to 1.63) | (0.70 to 0.78) | (0.58 to 1.05) | (0.10 to 1.08) | (0.38 to 2.19) | (1.67 to 3.68) | (0.88 to 0.99) | (0.77 to 0.82) | (0.82 to 2.05) |
| | | $< 2\times10^{-16}$ | $< 2\times10^{-16}$ | 0.103 | 0.067 | 0.83 | $6.5\times10^{-6}$ | 0.033 | $< 2\times10^{-16}$ | 0.27 |
| | | Amplifying (RI<1) | Inhibitory | Non-significant | Non-significant | Non-significant | Amplifying (RI<1) | Inhibitory | Inhibitory | Non-significant |
| DTaP/IPV/Hib+MenC+PCV | 3 | 1.93 | 1.31 | 1.25 | 13.87 | $1.53\times10^{+5}$ | 1.44 | 1.49 | 1.27 | 1.68 |
| | | (1.63 to 2.29) | (1.14 to 1.49) | (0.63 to 2.51) | (0.74 to 260.58) | ($2.16\times10^{-121}$ - $10.08\times10^{+131}$) | (0.53 to 3.92) | (1.29 to 1.74) | (1.17 to 1.38) | (0.56 to 5.09) |
| | | $4,77\times10^{-14}$ | $1.17\times10^{-4}$ | 0.523 | 0.079 | 0.936 | 0.471 | $1.64\times10^{-7}$ | $1.15\times10^{-8}$ | 0.356 |
| | | Amplifying | Amplifying | Non-significant | Non-significant | Non-significant | Non-significant | Amplifying | Amplifying | Non-significant |
| DTaP/IPV/Hib+MenC+ RV | 3 | 0.94 | 1.65 | 0.7 | $1.74\times10^{-7}$ | $1.47\times10^{-5}$ | 1.8 | 1.17 | 1.1 | 1.25 |
| | | (0.69 to 1.28) | (1.35 to 2.02) | (0.20 to 2.38) | (0.00-inf) | (0.00-inf) | (0.20 to 16.08) | (0.94 to 1.44) | (0.98 to 1.24) | (0.11 to 14.68) |
| | | 0.714 | $9.19\times10^{-7}$ | 0.565 | 0.994 | 0.988 | 0.6 | 0.152 | 0.099 | 0.858 |
| | | Non-significant | Amplifying | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant |
| DTaP/IPV/Hib+PCV | 2 | 0.74 | 0.75 | 0.8 | 0.14 | 0.87 | 0.95 | 0.74 | 0.82 | 1.26 |
| | | (0.70 to 0.78) | (0.72 to 0.79) | (0.61 to 1.05) | (0.05 to 0.39) | (0.37 to 2.06) | (0.71 to 1.28) | (0.71 to 0.78) | (0.80 to 0.84) | (0.87 to 1.83) |
| | | $< 2\times10^{-16}$ | $< 2\times10^{-16}$ | 0.103 | $1.45\times10^{-4}$ | 0.749 | 0.754 | $< 2\times10^{-16}$ | $< 2\times10^{-16}$ | 0.228 |
| | | Inhibitory | Inhibitory | Non-significant | Inhibitory | Non-significant | Non-significant | Inhibitory | Inhibitory | Non-significant |

Continued

**Table 4** Continued

| Vaccines coadministered | No of vaccines | RIR; (95% CI); p value; interaction | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Fever | Gastrointestinal | General symptoms | Local symptoms | Musculoskeletal | Neurological | Rash | Respiratory/ misc | Sensitivity/ anaphylaxis |
| DTaP/IPV/ Hib+PCV+ RV | 3 | 1.44 | 1.16 | 1.31 | $6.29\times10^{-7}$ | $2.43\times10^{-4}$ | 0.3 | 1.19 | 1.4 | 0.84 |
| | | (1.09 to 1.90) | (0.97 to 1.40) | (0.38 to 4.46) | (0.00-inf) | (0.00-inf) | (0.03 to 2.71) | (0.97 to 1.46) | (1.25 to 1.57) | (0.07 to 10.32) |
| | | 0.009 | 0.11 | 0.67 | 0.996 | 0.983 | 0.286 | 0.099 | $1.20\times10^{-8}$ | 0.893 |
| | | Amplifying | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Amplifying | Non-significant |
| DTaP/IPV/ Hib+RV | 2 | 1.62 | 0.71 | 0.49 | 0.55 | $1.39\times10^{-4}$ | 1.6 | 0.82 | 0.80 | 0.90 |
| | | (1.42 to 1.85) | (0.65 to 0.77) | (0.27 to 0.89) | (0.10 to 3.03) | ($2.02\times10^{-107}$ - $90.50\times10^{+114}$) | (0.78 to 3.29) | (0.74 to 0.90) | (0.75 to 0.84) | (0.30 to 2.63) |
| | | $4.36\times10^{-13}$ | $7.19\times10^{-16}$ | 0.019 | 0.491 | 0.942 | 0.204 | $3.6\times10^{-5}$ | $4.35\times10^{-16}$ | 0.842 |
| | | Amplifying (RI<1) | Inhibitory | Inhibitory | Non-significant | Non-significant | Non-significant | Inhibitory | Inhibitory | Non-significant |
| MMR+Hib/ MenC+PCV | 3 | 0.67 | 1.48 | 0.76 | 12.98 | 0.07 | 0.86 | 1.08 | 1.43 | 0.5 |
| | | (0.55 to 0.80) | (1.20 to 1.82) | (0.26 to 2.22) | (0.00-inf) | (0.01 to 0.41) | (0.36 to 2.06) | (0.87 to 1.34) | (1.26 to 1.63) | (0.20 to 1.28) |
| | | $2.01\times10^{-5}$ | $2.15\times10^{-4}$ | 0.614 | 1 | 0.003 | 0.741 | 0.472 | $8.64\times10^{-8}$ | 0.15 |
| | | Inhibitory | Amplifying | Non-significant | Non-significant | Inhibitory | Non-significant | Non-significant | Amplifying | Non-significant |
| MMR+PCV | 2 | 1.91 | 0.76 | 0.9 | 0.21 | 1.56 | 2.04 | 1.06 | 0.79 | 1.22 |
| | | (1.83 to 1.99) | (0.72 to 0.80) | (0.72 to 1.13) | (0.08 to 0.54) | (0.85 to 2.88) | (1.67 to 2.49) | (1.01 to 1.11) | (0.77 to 0.81) | (0.94 to 1.58) |
| | | $< 2\times10^{-16}$ | $< 2\times10^{-16}$ | 0.381 | 0.013 | 0.152 | $3.13\times10^{-12}$ | 0.018 | $< 2\times10^{-16}$ | 0.144 |
| | | Amplifying | Inhibitory | Non-significant | Inhibitory | Non-significant | Amplifying | Amplifying | Inhibitory | Non-significant |
| (B) RIR and interaction effects of the adverse events for all never recommended coadministrations studied | | | | | | | | | | |
| DTaP/IPV or dTaP/IPV+Hib/ MenC | 2 | 0.52 | 0.73 | 0.76 | – | 0.84 | 1.01 | 0.98 | 0.63 | 1.00 |
| | | (0.35 to 0.77) | (0.45 to 1.18) | (0.24 to 2.42) | – | (0.20 to 3.55) | (0.32 to 3.24) | (0.52 to 1.12) | (0.50 to 0.80) | (0.24 to 4.11) |
| | | 0.001 | 0.198 | 0.645 | – | 0.812 | 0.982 | 0.161 | 0.0001 | 0.997 |
| | | Inhibitory | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Inhibitory | Non-significant |
| DTaP/IPV or dTaP/IPV+ MMR + Hib/MenC | 3 | 0.80 | 0.65 | 1.11 | – | 0.64 | 0.70 | 1.04 | 1.08 | 0.59 |
| | | (0.37 to 1.75) | (0.25 to 1.72) | (0.10 to 12.89) | – | (0.04 to 11.67) | (0.06 to 8.38) | (0.48 to 2.27) | (0.66 to 1.76) | (0.03 to 10.24) |
| | | 0.578 | 0.388 | 0.934 | – | 0.766 | 0.778 | 0.925 | 0.760 | 0.720 |
| | | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant |
| DTaP/IPV or dTaP/IPV+PCV | 2 | 0.40 | 0.90 | 1.12 | $2.78\times10^{-8}$ | $1.11\times10^{-4}$ | 0.58 | 0.77 | 0.79 | 0.85 |
| | | (0.30 to 0.54) | (0.76 to 1.06) | (0.41 to 3.03) | (0.00-inf) | ($5.11\times10^{-135}$ to $20.40\times10^{+126}$) | (0.18 to 1.86) | (0.62 to 0.96) | (0.71 to 0.87) | (0.27 to 2.72) |
| | | $3.66\times10^{-10}$ | 0.192 | 0.831 | 0.995 | 0.953 | 0.362 | 0.019 | $1.11\times10^{-5}$ | 0.789 |
| | | Inhibitory | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Inhibitory | Inhibitory | Non-significant |

Continued

**Table 4** Continued

| Vaccines coadministered | No of vaccines | RIR; (95% CI); p value; interaction | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Fever | Gastrointestinal | General symptoms | Local symptoms | Musculoskeletal | Neurological | Rash | Respiratory/ misc | Sensitivity/ anaphylaxis |
| DTaP/IPV/Hib + MenB+MenC + RV | 4 | 2.18 | 1.00 | $4.61\times10^{-5}$ | – | – | $1.56\times10^{-4}$ | 0.65 | 0.57 | $4.24\times10^{-4}$ |
| | | (0.42 to 11.21) | (0.33 to 3.07) | ($4.06\times10^{-260}$ to $50.23\times10^{+270}$) | – | – | (0.00-inf) | (0.24 to 1.75) | (0.30 to 1.05) | (0.00-inf) |
| | | 0.351 | 0.998 | 0.967 | – | – | 0.991 | 0.390 | 0.073 | 0.990 |
| | | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant |
| DTaP/IPV/Hib+MMR | 2 | 1.18 | 0.59 | 1.26 | $2.10\times10^{-7}$ | 3.56 | 1.48 | 0.84 | 0.63 | 1.78 |
| | | (0.92 to 1.52) | (0.45 to 0.78) | (0.62 to 0.2.56) | (0.00-inf) | (1.21 to 10.50) | (0.55 to 4.00) | (0.64 to 1.09) | (0.55 to 0.73) | (0.72–4.38) |
| | | 0.186 | 0.0002 | 0.523 | 0.993 | 0.021 | 0.442 | 0.187 | $1.71\times10^{-9}$ | 0.209 |
| | | Non-significant | Inhibitory | Non-significant | Non-significant | Amplifying | Non-significant | Non-significant | Inhibitory | Non-significant |
| MMR+MenB + MenC+ PCV | 4 | 5585 | 2388 | – | – | – | $8.73\times10^{-11}$ | 3029 | – | – |
| | | ($5.71\times10^{-112}$ to $50.47\times10^{+118}$) | ($9.26\times10^{-158}$ to $60.16\times10^{+163}$) | – | – | – | (0.00 to inf) | ($4.53\times10^{-105}$ to $20.02\times10^{+111}$) | – | – |
| | | 0.949 | 0.967 | – | – | – | 0.992 | 0.950 | – | – |
| | | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant |
| MMR+MenC | 2 | 1.58 | 0.65 | 0.55 | $4.19\times10^{-8}$ | 2.33 | 0.73 | 0.97 | 0.71 | 0.98 |
| | | (1.37 to 1.82) | (0.55 to 0.76) | (0.23 to 1.34) | (0.00 to inf) | (0.81 to 6.66) | (0.27 to 1.98) | (0.85 to 1.11) | (0.65 to 0.78) | (0.31–3.11) |
| | | $1.57\times10^{-10}$ | $1.18\times10^{-7}$ | 0.188 | 0.994 | 0.116 | 0.538 | 0.664 | $1.09\times10^{-13}$ | 0.974 |
| | | Amplifying | Inhibitory | non-significant | non-significant | non-significant | non-significant | non-significant | Inhibitory | non-significant |
| MMR+MenC + PCV | 3 | 0.37 | 1.68 | 11.83 | 1.85 | $3.89\times10^{-4}$ | 0.24 | 1.27 | 1.07 | 0.64 |
| | | (0.27 to 0.51) | (1.07 to 2.64) | (1.28 to 109.01) | (0.00 to inf) | ($5.81\times10^{-99}$ to $20.6\times10^{+91}$) | (0.02 to–2.37) | (0.83 to 1.94) | (0.85 to 1.34) | (0.06–7.46) |
| | | $1.81\times10^{-9}$ | 0.023 | 0.029 | 1 | 0.944 | 0.221 | 0.27 | 0.554 | 0.722 |
| | | Inhibitory | Amplifying | Amplifying | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant |
| MMR+Td/IPV | 2 | 1.11 | 1.00 | 1.26 | – | 0.71 | 0.77 | 1.05 | 0.88 | 1.82 |
| | | (0.78 to 1.57) | (0.70 to 1.43) | (0.79 to 2.01) | – | (0.31 to–1.63) | (0.22 to 2.73) | (0.79 to 1.41) | (0.74 to 1.04) | (0.77-.4.27) |
| | | 0.563 | 0.982 | 0.336 | – | 0.423 | 0.69 | 0.723 | 0.128 | 0.171 |
| | | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant |
| Td/IPV+HPV | 2 | 1.29 | 0.65 | 0.84 | – | 1.14 | 4.5 | 0.37 | 1.14 | $5.07\times10^{-5}$ |
| | | (0.17 to 9.51) | (0.09 to 4.73) | (0.37 to 1.89) | – | (0.42 to 3.08) | (0.56 to–36.15) | (0.05 to 2.68) | (0.59 to 2.22) | ($2.64\times10^{-201}$ -$90.72\times10^{+191}$) |
| | | 0.805 | 0.673 | 0.677 | – | 0.801 | 0.157 | 0.328 | 0.694 | 0.966 |
| | | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant | Non-significant |

IPV/Hib+MenC+RV compared with separate administration, which were also detected in another study, together with general symptoms.[16 36] DTaP/IPV/Hib+PCV+RV led to more fever and respiratory events compared with separate administration. Fever, local and general symptoms, and gastrointestinal events were often reported in another study on DTaP/IPV/Hib+PCV+RV coadministration.[37] Also studies on DTaP/IPV/Hib/HepB+PCV+RV reported mostly fever, local reactions, respiratory and gastrointestinal events.[38 39] MMR+Hib/MenC+PCV led to more gastrointestinal, and respiratory events and less fever and musculoskeletal events than would have been expected based on separate vaccinations. One clinical trial on this coadministration did not detect differences for local or systemic adverse events compared with separate administrations.[40] One of the unscheduled coadministrations of three vaccines—MMR+MenC+PCV—led to more than expected gastrointestinal events and general symptoms and less fever. No other studies investigated the safety of the unscheduled coadministrations of three vaccines. One scheduled coadministration of two vaccines—MMR+PCV led to more fever, neurological events, and rash compared with separate administration. One other study reported lower[40] and another one higher proportions[41] of fever, while the other AEFIs were not specifically assessed or reported in these and other studies on MMR+PCV.[16 40–42] Also the unscheduled coadministrations of DTaP/IPV/Hib+MMR caused more musculoskeletal events and MMR+MenC more fever than expected. One study reported an increase in overall AE following DTaP/IPV/Hib+MMR[16 43] and another detected increased AE following coadministrations of MMR+MenC, particularly febrile seizures.[44]

For coadministrations of two vaccines, we detected amplifying interaction effects for events that had an RI<1 following vaccination and thus occurred less following immunisation than in the control period. Although the RIs of these events were higher following coadministration than would have been expected based on separate administration of these vaccines, they still occurred less than in the control period (RI<1). This indicates that vaccination has a protective effect that is reduced following coadministration. Such observations have not been documented before, although some other studies reported increased reactogenicity for some of these coadministrations. We found a reduced protective effect for fever and neurological events following DTaP/IPV/Hib+MenC, and fever after DTaP/IPV/Hib+RV. Other studies assessing the safety of these coadministrations found no differences between coadministration and separate administration.[16 45–47] Coadministering two vaccines led to less AEFI than expected based on the RIs after separate administration for 28% of analysed AEFI. The aforementioned literature review also found reports of such a inhibitory effect of vaccine coadministration on diarrhoea and fever following DTaP/IPV+RV,[48] erythema following DTaP/IPV/Hib/HepB+MenC,[49] and nasopharyngitis and insomnia following MMRV+PCV.[5016]

Adding a fourth vaccine did not significantly alter the reactogenicity for the studied AEFI. To date, no other studies are available on the two unscheduled coadministrations of four vaccines included in our study.

Based on the RIR alone, our observations underpin the safety of coadministration of two scheduled routine paediatric vaccines. Our findings also indicate that adding a third vaccine may lead to a greater burden due to AEFI, in line with previous studies.[16] Either way, we recommend further research into the severity of these events following separate versus coadministration for a more comprehensive assessment of the burden caused by these events and to evaluate whether the benefits of coadministration outweigh its risks. For example by augmenting routine data collection with questionnaires and/or other data sources, as has been conducted in influenza vaccination,[51] and including supplementary data such as hospital admissions and deaths.

We found no indications that never recommended coadministrations per se are less safe than recommended coadministrations. Two recommended (DTaP/IPV/Hib+PCV, DTaP/IPV or dTaP/IPV+MMR) and four never recommended (DTaP/IPV or dTaP/IPV+Hib/MenC, DTaP/IPV or dTaP/IPV+PCV, MMR+Td/IPV, Td/IPV+HPV) coadministrations of two vaccines did not lead to more AEFI, which is in line with other studies' findings.[16 46 52–54] One recommended (DTaP/IPV/Hib+MenB + PCV) and one never recommended (DTaP/IPV or dTaP/IPV+MMR + Hib/MenC) did not increase AEFI either. However, one study reported more fever, a higher reactogenicity for local and general symptoms (irritability) after DTaP/IPV/Hib+MenB + PCV.[55] Also the unscheduled addition of a fourth vaccine did not lead to more AEFIs and we found no studies reporting safety concerns. Nevertheless, unscheduled coadministrations happen occasionally and hence data on AEFI following such coadministrations may be too limited to identify significant differences between separate and coadministrations.

To the best of our knowledge, this is the first real-life data study comparing the safety of coadministering vaccines vs the safety of separately administering the same vaccines in two scenarios: administration as recommended in the immunisation schedule and never recommended. We chose the SCCS method to control for between-person confounders by comparing the risk and reference periods in each patient. We used a 42-day exposure period corresponding to risk periods commonly used in vaccine pharmacovigilance studies and appropriate for hypothesis generating studies since it reassures capturing nearly all AEFI.[56] The SCCS method requires only cases to provide consistent estimates of the RI and controls implicitly for fixed confounders.[29 31] SCCS estimate RIs, comparing the incidences of adverse events in exposure periods to unexposed periods within persons.[31] This is particularly useful for studying vaccines with high coverage for which unvaccinated controls may be hard to find.[31] However, no estimates of absolute incidence can

be obtained.[29] Therefore, we recommend researchers to compare the incidences between separate and coadministration on the same data using other methods. The large quantity of real-life vaccination and event data allows for powerful analyses. However, data from medical records may be prone to misclassification and heterogeneous as they are recorded by different persons to document and inform medical practice and not specifically for this study. The data may be prone to reporting bias because parents may consult their GP related to AEFI differently than when such events would manifest without prior vaccination, which may lead to lower RIs. Relying on existing medical records limits analysis to the availability of variables captured in the database.[57] Consequently, we invite researchers to replicate this study by using the same method but on different data from other sources. Given the emerging insights on non-specific effects of vaccinations and calls for studying the influence of the order of vaccinations on such effects,[58] we advise to widen the research focus to address the potential influence of vaccine coadministrations on such non-specific effects as well.

The implementation of coadministration practices should be supported by evidence that coadministered vaccines are at least equally safe as separately administered vaccines. Real-life data show that coadministrations of two vaccines have an equal or even better safety profile than administering the respective vaccines separately, but adding a third vaccine can increase the incidence of AEFI. We call for enhanced surveillance for a more comprehensive evaluation of the risks associated with vaccine coadministrations, and whether such risks are outweighed by the benefits of coadministration.

**Contributors** JB planned, designed, conducted the study and analyses, wrote the manuscrip, and is the guarantor; SdL and NK served as scientific advisors and critically reviewed the manuscript, YGW served as scientific advisor for the SCCS method and critically reviewed the manuscript; JB planned this study, served as scientific advisor, critically reviewed the study proposal and manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This research was exempt from ethical approval. The research proposal and data request were evaluated and accepted by the RCGP RSC. No other approvals were required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available. Data used for this study remains stored on secure servers of the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), and can be accessed on the RCGP RSC conditions.



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# 5. Main results

## 5.1. Study population

The study cohort was representative for the paediatric population in the RCGP RSC database with similar distributions between genders, regions, and relative deprivation on both the individual level and exposure level. [13]

## 5.2. Exposure

We analysed data from 6 257 828 doses for 15 182 366 antigens, covered by the 13 routine paediatric vaccines listed in Public Health England's paediatric immunisation schedule between 2008 and 2018. [13]

## 5.3. Timeliness of paediatric immunisations

We found that 75% of first vaccination doses were administered on time, and 51% of second doses and 45% of third doses followed timely after the preceding dose. [13] Altogether, 20% of children received all their routine vaccines on time. [13] First doses were rarely given too early (6%), while subsequent doses were often given sooner than scheduled after the preceding dose (36% of second and 37% of third doses). [13] Overall, 19% of first doses were administered too late and 13% of second and 18% of third doses longer than scheduled after the preceding dose. [13] The timeliness of all vaccines and doses is detailed in Figure 2. The median deviations from the recommended ages ranged between 0 and 1 month (IQR between 0 and 2 months for first doses, IQR between -2 and 2 months for subsequent doses), except for DTaP/IPV or dTaP/IPV (median 2 months; IQR 0 to 5), Td/IPV (median 1 month; IQR -1 to 13), and MenACWY (median 29 months; IQR 6 to 55). [13]

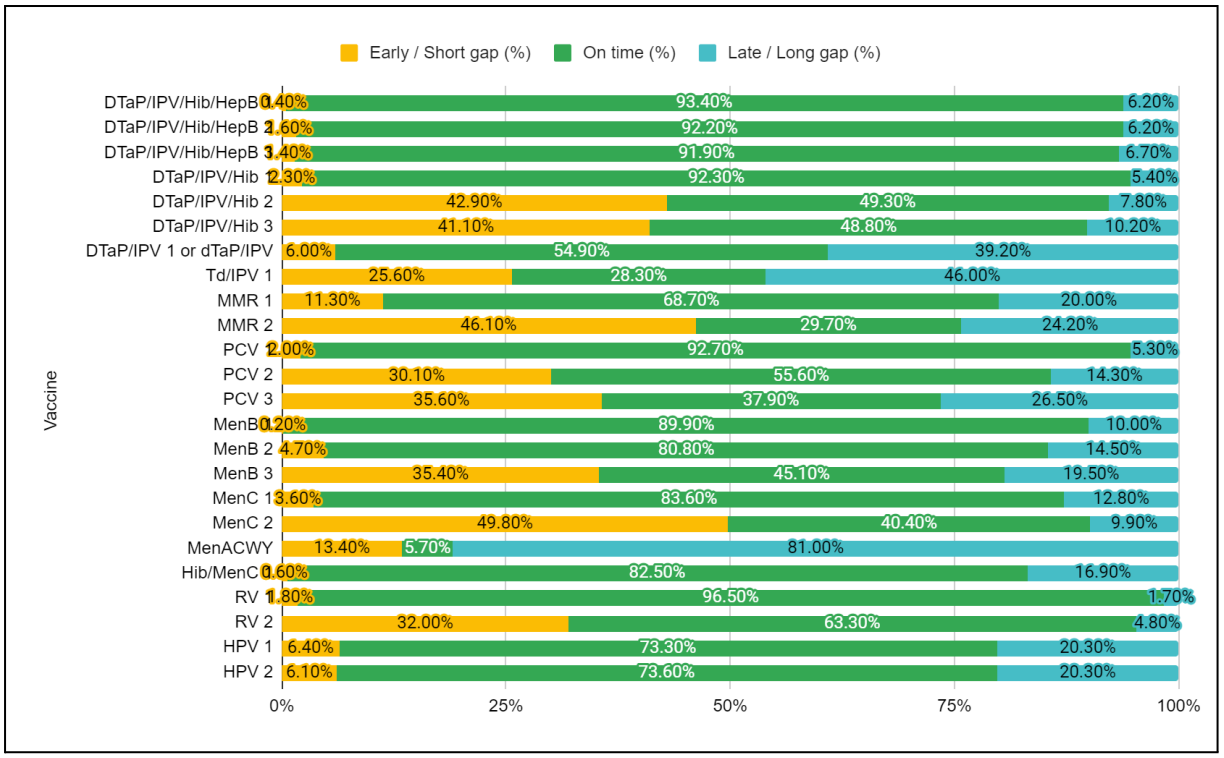


***Figure 2.*** *Timelines of routine paediatric vaccines.*

We detected significant associations ($p<0.05$) between decreasing deprivation and improved schedule adherence for most vaccines and doses. [13] There were small differences in immunisation schedule adherence between North England, the Midlands and East England, London and South England and the timeliness of vaccinations was similar for girls and boys. [13]

## 5.4. Vaccine co-administration

Seventy-nine percent of all routine paediatric vaccines were co-administered: 36% of vaccines were administered together with a second vaccine; 33% were co-administrations of three vaccines, and 9% were co-administrations of four vaccines. [3] 5 782 118 vaccines in our study were scheduled for co-administration with one or more other vaccines (i.e. all routine paediatric vaccines except HPV). [3] Of those, 64% were co-administered with other vaccines and doses as recommended, while 15% were administered separately. [3] Eighteen percent of these vaccines were co-administered with other doses of the recommended vaccines, lacked at least one of the vaccines recommended to be given at the same time, or were co-administered according to an outdated schedule. [3] Three percent of these vaccine co-administrations were never scheduled together. [3] Figure 3 shows the proportions of all

vaccine doses co-administered as recommended, as deviated co-administrations, as never recommended co-administrations, or given separately. Fifty-two percent of the children received all their co-administered vaccines exactly as recommended in the immunisation schedule, while 19% received none of their vaccines co-administered as recommended. [3]

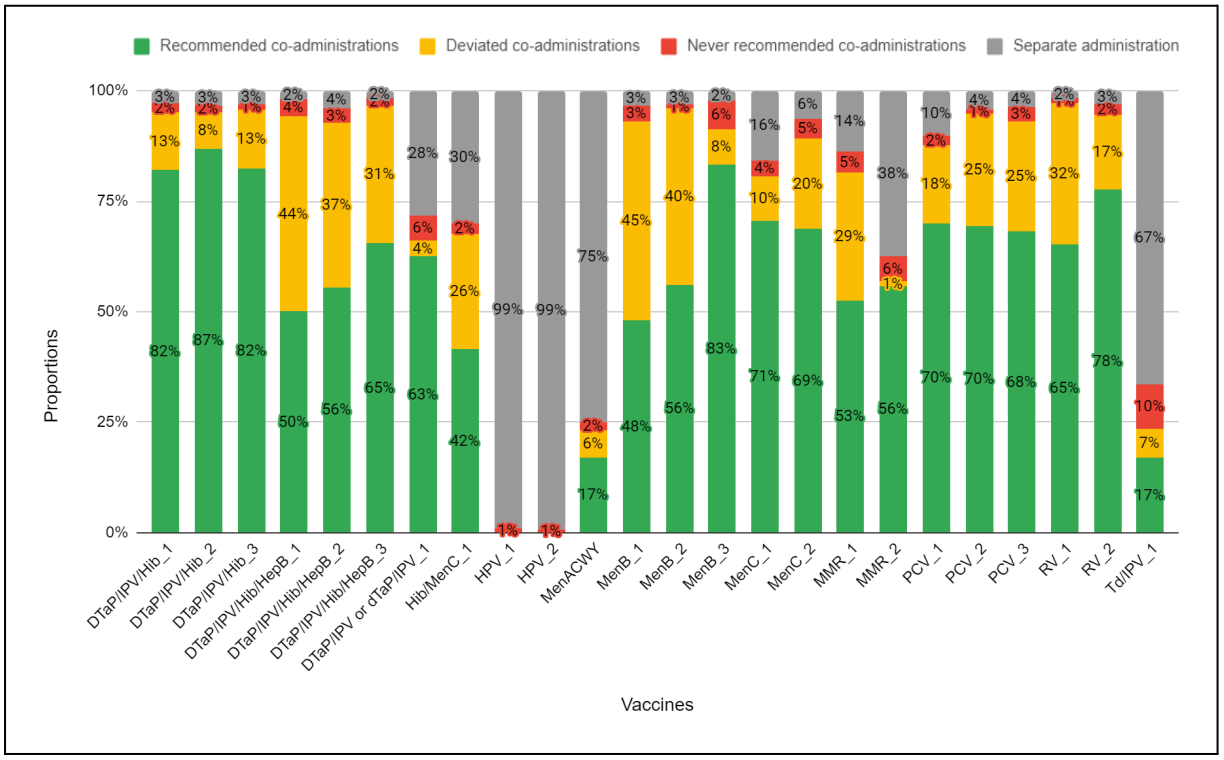


***Figure 3.*** *Proportions of routine paediatric vaccine doses co-administered with other vaccines as recommended, deviated, or never recommended in the immunisation schedule, or given separately. [3]*

Altogether, 75% of routine paediatric vaccine co-administrations were given as listed in the immunisation schedule, while 4% were never recommended. The remaining 21% of co-administrations deviated from the recommendations: 10% were co-administrations according to an outdated schedule, 7% concerned co-administrations lacking at least one vaccine compared to the schedule, 3% had shifted doses, and 1% were outdated co-administrations and had shifted doses. [3] The ten most often recommended, deviated, and never recommended co-administrations are presented in Table 2.

***Table 2.*** *The most often co-administered vaccines during the study period (2008 - 2018), by category (percentages indicate the proportion of each vaccine co-administration on the total number of co-administrations). [3]*

| **Co-administrations as listed in the schedule**[1] | **n** | **%** | **Recommended ages**[2] |
|---|---|---|---|
| DTaP/IPV/Hib + PCV | 274 919 | 13.9% | 8 weeks; 16 weeks |
| DTaP/IPV or dTaP/IPV + MMR | 205 362 | 10.4% | 40 months |
| DTaP/IPV/Hib + MenC | 194 083 | 9.8% | 3 months; 4 months |
| DTaP/IPV/Hib + MenC + PCV | 180 688 | 9.2% | 4 months |
| Hib/MenC + MMR + PCV | 148 218 | 7.5% | 1 year |
| MMR + PCV | 91 134 | 4.6% | 1 year |
| DTaP/IPV/Hib + MenC + RV | 89 332 | 4.5% | 3 months |
| DTaP/IPV/Hib + PCV + RV | 74 704 | 3.8% | 2 months |
| DTaP/IPV/Hib + MenB + PCV | 42 154 | 2.1% | 8 weeks; 16 weeks; 1 year |
| DTaP/IPV/Hib + RV | 40 668 | 2.1% | 8 weeks; 12 weeks |
| **Deviated co-administrations**[3] | **n** | **%** | **Recommended ages** |
| Hib/MenC + MMR + PCV | 52 121 | 2.6% | 1 year |
| MenC + PCV | 43 965 | 2.2% | 4 months |
| Hib/MenC + MMR | 41 995 | 2.1% | 1 year |
| MMR + PCV | 35 025 | 1.8% | 1 year |
| DTaP/IPV/Hib + MenB + PCV | 29 183 | 1.5% | 8 weeks; 16 weeks; 1 year |
| DTaP/IPV/Hib + MenB + PCV + RV | 28 872 | 1.5% | 8 weeks |
| DTaP/IPV/Hib + PCV | 23 602 | 1.2% | 8 weeks; 16 weeks |
| DTaP/IPV/Hib + MenC | 21 005 | 1.1% | 3 months; 4 months |
| DTaP/IPV/Hib/HepB + MenB + PCV + RV | 14 309 | 0.7% | 8 weeks |

[1] Vaccines co-administered exactly as recommended in the immunisation schedule.

[2] Recommended ages for co-administering the vaccines according to the most recent immunisation schedule during the study period.

[3] Vaccine co-administrations deviating from the actual immunisations schedule.

| | | | |
|---|---|---|---|
| DTaP/IPV/Hib + MenC + PCV | 12 509 | 0.6% | 4 months |
| **Co-administrations never recommended[4]** | **n** | **%** | **Recommended ages[5]** |
| MMR + Td/IPV | 10 927 | 0.6% | See Figure 1 |
| MenC + MMR + PCV | 8 779 | 0.4% | See Figure 1 |
| DTaP/IPV/Hib + MMR | 7 452 | 0.4% | See Figure 1 |
| DTaP/IPV or dTaP/IPV + PCV | 6 800 | 0.3% | See Figure 1 |
| MenC + MMR | 4 922 | 0.2% | See Figure 1 |
| DTaP/IPV or dTaP/IPV + Hib/MenC + MMR | 2 834 | 0.1% | See Figure 1 |
| DTaP/IPV/Hib + MenB + MenC + RV | 2 748 | 0.1% | See Figure 1 |
| DTaP/IPV or dTaP/IPV + Hib/MenC | 2 127 | 0.1% | See Figure 1 |
| MenB + MenC + MMR + PCV | 1 630 | 0.1% | See Figure 1 |
| HPV + Td/IPV | 1 273 | 0.1% | See Figure 1 |

Associations between vaccine co-administrations and genders, IMD quintiles, NHS regions, and the timeliness of vaccinations were significant but small ($p<0.05$), as shown in Figures 4 and 5. [3] The OR for co-administrations as recommended when all vaccines were given on time was 2.46 (95% CI 2.44-2.48), while the odds for deviated co-administrations (OR 1.60; 95% CI 1.58-1.62) and co-administrations that were never recommended (OR 5.34; 95% CI 5.19-5.50) increased when at least one vaccine was given too late (OR 1.60; 95% CI 1.58-1.62). [3]

[4] Vaccine co-administrations that were never recommended.
[5] The recommended ages for each of these vaccinations is listed in Figure 1 for the most recent immunisation schedule during the study period.

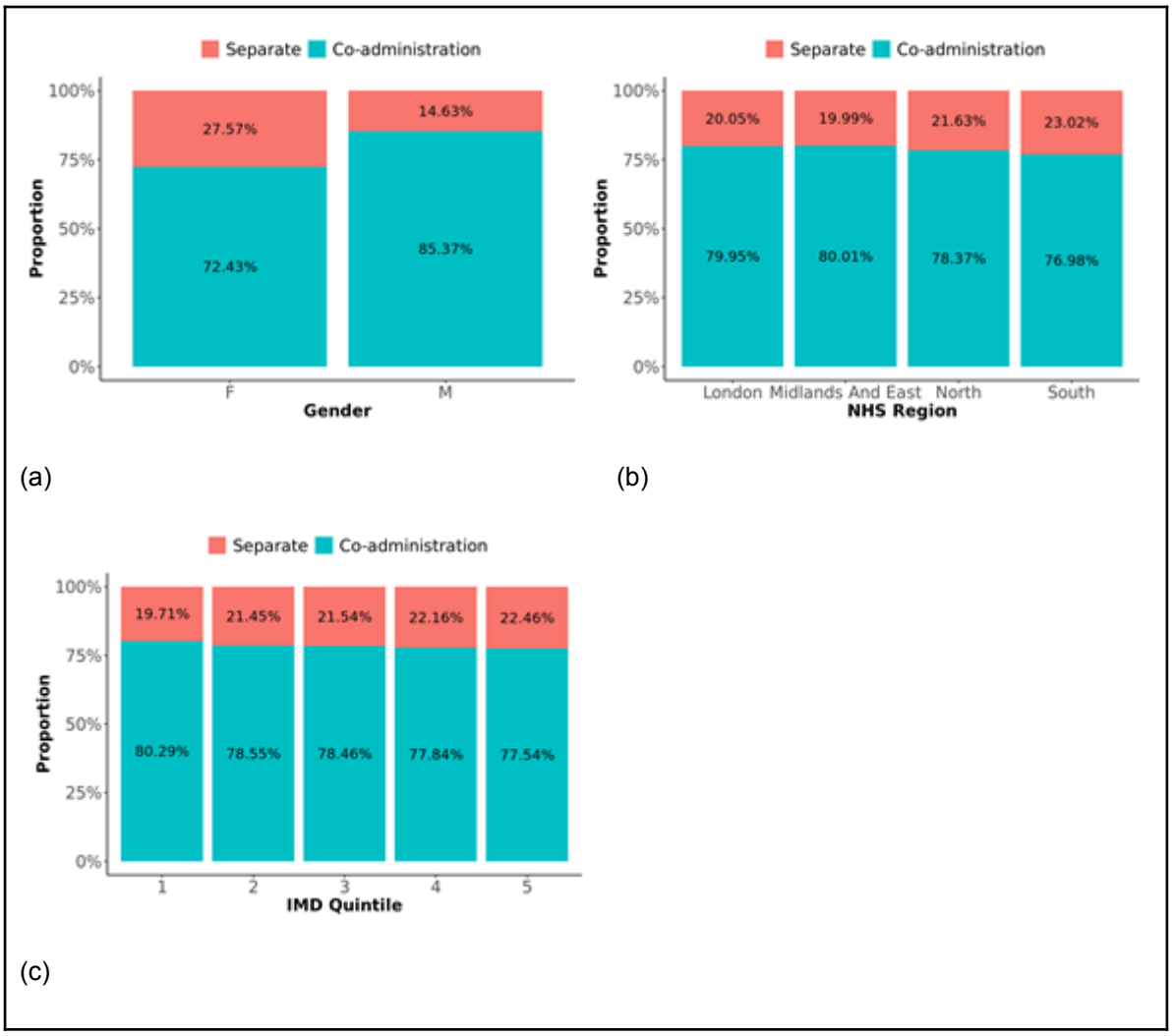


***Figure 4*** *a-c. Co-administration ratios of routine paediatric vaccines, by gender, NHS region, and IMD quintile (percentages indicate the proportions of all vaccines that were administered separately or co-administered with at least one other vaccine).*

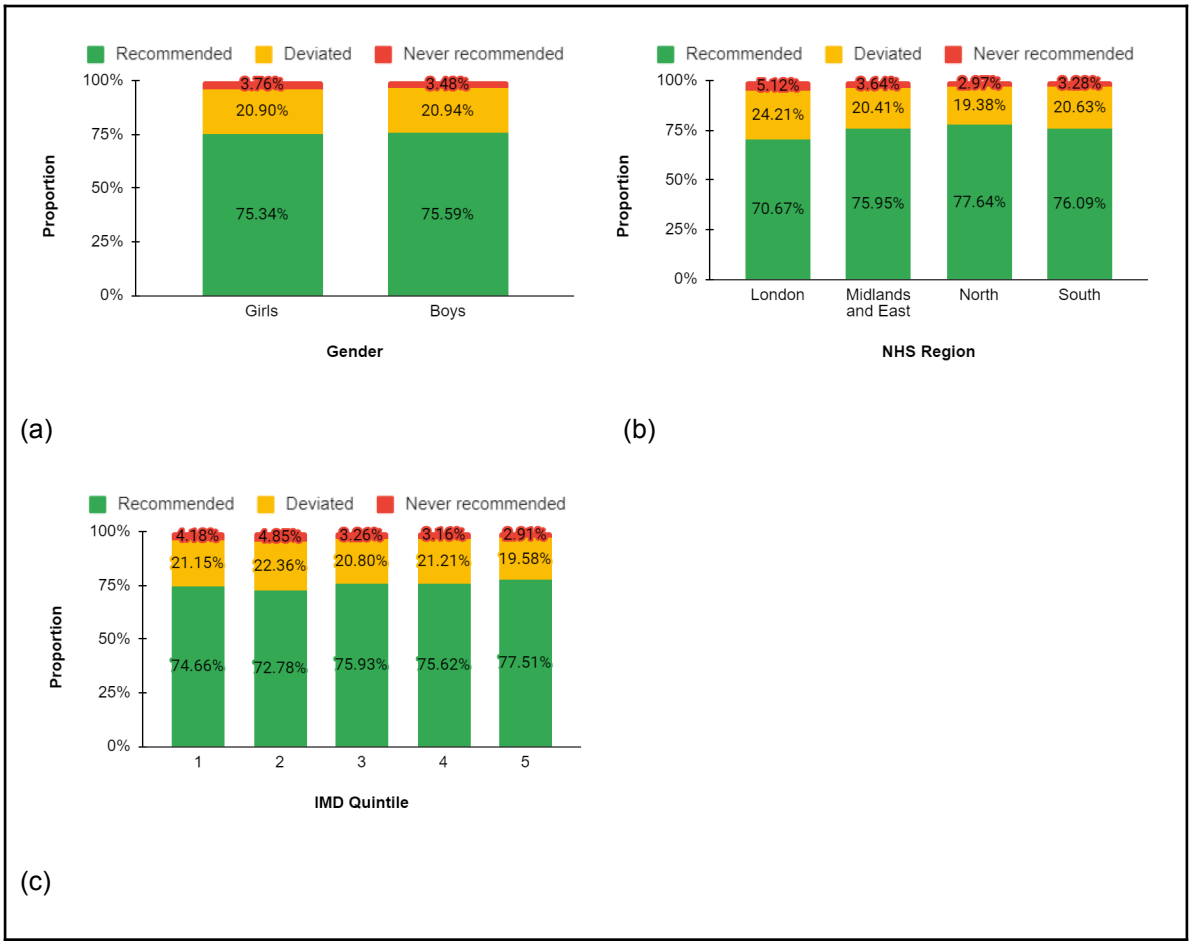


***Figure 5*** *a-c. Overall co-administration ratios of routine paediatric vaccines co-administered as recommended, deviated, or as never recommended in any immunisation schedule during the study period, by gender, NHS region, and IMD quintile.*

## 5.5. Safety assessment

The safety assessment was done for the ten most frequent vaccine co-administrations according to the immunisation schedule and the ten most frequent never recommended vaccine co-administrations, asl listed in Table 2, using data from 5 993 290 vaccine doses for 13 920 730 antigens. [46] The 33 selected adverse events were grouped into nine types of AEFI, adding up to 3 518 047 events:

- Fever/Pyrexia: Fever symptoms, Mild fever (≤38.5°C), Moderat fever (38.6-39.5°C), High fever (>39.5°C)
- Gastrointestinal: Diarrhoea, Loss of appetite, Nausea, Vomiting
- General symptoms: Drowsiness, Fatigue, Headache, Malaise, Irritable
- Local symptoms: Local erythema

- Musculoskeletal: Myalgia, Post-immunisation arthropathy
- Neurological: Bell's Palsy, Convulsion/Febrile convulsion, Guillain-Barre Syndrome, Tremor
- Rash
- Respiratory/Miscellaneous: Acute conjunctivitis, Acute coryza, Cough, Epistaxis, Hoarse, Nasal airway obstruction, Rhinorrhoea, Sore mouth/Throat pain, Wheezing
- Sensitivity/anaphylaxis: Adverse drug reaction/Vaccine allergy, Drug-induced anaphylaxis, Facial swelling. [46]

The relative incidence ratios (RIR) for every analysed AEFI are listed in Tables 3 to 5 for each included co-administration. A RIR > 1 indicates an amplifying interaction effect while a RIR < 1 indicates an inhibitory interaction effect.

### 5.5.1. Safety of co-administering two vaccines

Co-administering MMR + PCV was followed by more cases of fever, rash, and neurological events, DTaP/IPV/Hib + MMR by more musculoskeletal events, and MMR + MenC by more cases of fever (see Table 3). [46] Also the RIs of fever and neurological events following DTaP/IPV/Hib + MenC and fever following DTaP/IPV/Hib + RV increased compared to separate vaccination but remained below 1 and thus occurred less following vaccination. [46] Beyond these, co-administrations of two vaccines had no or an inhibitory interaction effect on the RIs of the analysed events (see Table 3). [46]

***Table 3.*** *Relative incidence ratios (RIR) and interaction effects of AEFI for co-administrations of two vaccines. [46]*

| **Vaccines co-administered** | **Recomm.** | **RIR; [confidence interval]; interaction** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Fever** | **Gastro-intestinal** | **General symptoms** | **Local symptoms** | **Musculo-skeletal** | **Neurological** | **Rash** | **Respiratory / Misc.** | **Sensitivity / Anaphylaxis** |
| DTaP/IPV or dTaP/IPV + MMR | Yes | 0.76 | 0.76 | 1.24 | 0.42 | 1.09 | 1.12 | 0.78 | 0.87 | 1.00 |
| | | [0.70-0.82] | [0.68-0.84] | [0.85-1.80] | [0.09-1.90] | [0.71-1.68] | [0.68-1.84] | [0.71-0.87] | [0.83-0.92] | [0.63-1.59] |
| | | Inhibitory | Inhibitory | non-significant | non-significant | non-significant | non-significant | Inhibitory | Inhibitory | non-significant |
| DTaP/IPV/Hib + MenC | Yes | 1.51 | 0.74 | 0.78 | 0.33 | 0.91 | 2.48 | 0.94 | 0.8 | 1.29 |
| | | [1.41-1.63] | [0.70-0.78] | [0.58-1.05] | [0.10-1.08] | [0.38-2.19] | [1.67-3.68] | [0.88-0.99] | [0.77-0.82] | [0.82-2.05] |
| | | Amplifying (RI < 1) | Inhibitory | non-significant | non-significant | non-significant | Amplifying (RI < 1) | Inhibitory | Inhibitory | non-significant |
| DTaP/IPV/Hib + PCV | Yes | 0.74 | 0.75 | 0.8 | 0.14 | 0.87 | 0.95 | 0,74 | 0.82 | 1.26 |
| | | [0.70-0.78] | [0.72-0.79] | [0.61-1.05] | [0.05-0.39] | [0.37-2.06] | [0.71-1.28] | [0.71-0.78] | [0.80-0.84] | [0.87-1.83] |
| | | Inhibitory | Inhibitory | non-significant | Inhibitory | non-significant | non-significant | Inhibitory | Inhibitory | non-significant |
| DTaP/IPV/Hib + RV | Yes | 1.62 | 0.71 | 0.49 | 0.55 | $1.39\times10^{4}$ | 1.6 | 0.82 | 0.80 | 0.90 |
| | | [1.42-1.85] | [0.65-0.77] | [0.27-0.89] | [0.10-3.03] | [$2.02\times10^{-107}$ - $9.50\times10^{114}$] | [0.78-3.29] | [0.74-0.90] | [0.75-0.84] | [0.30-2.63] |
| | | Amplifying (RI < 1) | Inhibitory | Inhibitory | non-significant | non-significant | non-significant | Inhibitory | Inhibitory | non-significant |
| MMR + PCV | Yes | 1.91 | 0.76 | 0.9 | 0.21 | 1.56 | 2.04 | 1.06 | 0.79 | 1.22 |
| | | [1.83-1.99] | [0.72-0.80] | [0.72-1.13] | [0.08-0.54] | [0.85-2.88] | [1.67-2.49] | [1.01-1.11] | [0.77-0.81] | [0.94-1.58] |
| | | Amplifying | Inhibitory | non-significant | Inhibitory | non-significant | Amplifying | Amplifying | Inhibitory | non-significant |

| Vaccines co-administered | Recomm. | RIR; [confidence interval]; interaction | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Fever** | **Gastro-intestinal** | **General symptoms** | **Local symptoms** | **Musculo-skeletal** | **Neurological** | **Rash** | **Respiratory / Misc.** | **Sensitivity / Anaphylaxis** |
| DTaP/IPV or dTaP/IPV + Hib/MenC | Never | 0.52 | 0.73 | 0.76 | - | 0.84 | 1.01 | 0.98 | 0.63 | 1.00 |
| | | [0.35-0.77] | [0.45-1.18] | [0.24-2.42] | - | [0.20-3.55] | [0.32-3.24] | [0.52-1.12] | [0.50-0.80] | [0.24-4.11] |
| | | Inhibitory | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | Inhibitory | non-significant |
| DTaP/IPV or dTaP/IPV + PCV | Never | 0.40 | 0.90 | 1.12 | $2.78\times10^{-8}$ | $1.11\times10^{-4}$ | 0.58 | 0.77 | 0.79 | 0.85 |
| | | [0.30-0.54] | [0.76-1.06] | [0.41-3.03] | [0.00-inf] | [$5.11\times10^{-135}$ - $2.40\times10^{126}$] | [0.18-1.86] | [0.62-0.96] | [0.71-0.87] | [0.27-2.72] |
| | | Inhibitory | non-significant | non-significant | non-significant | non-significant | non-significant | Inhibitory | Inhibitory | non-significant |
| DTaP/IPV/Hib + MMR | Never | 1.18 | 0.59 | 1.26 | $2.10\times10^{-7}$ | 3.56 | 1.48 | 0.84 | 0.63 | 1.78 |
| | | [0.92-1.52] | [0.45-0.78] | [0.62-0.2.56] | [0.00-inf] | [1.21-10.50] | [0.55-4.00] | [0.64-1.09] | [0.55-0.73] | [0.72-4.38] |
| | | non-significant | Inhibitory | non-significant | non-significant | Amplifying | non-significant | non-significant | Inhibitory | non-significant |
| MMR + MenC | Never | 1.58 | 0.65 | 0.55 | $4.19\times10^{-8}$ | 2.33 | 0.73 | 0.97 | 0.71 | 0.98 |
| | | [1.37-1.82] | [0.55-0.76] | [0.23-1.34] | [0.00-inf] | [0.81-6.66] | [0.27-1.98] | [0.85-1.11] | [0.65-0.78] | [0.31-3.11] |
| | | Amplifying | Inhibitory | non-significant | non-significant | non-significant | non-significant | non-significant | Inhibitory | non-significant |
| MMR + Td/IPV | Never | 1.11 | 1.00 | 1.26 | - | 0.71 | 0.77 | 1.05 | 0.88 | 1.82 |
| | | [0.78-1.57] | [0.70-1.43] | [0.79-2.01] | - | [0.31-1.63] | [0.22-2.73] | [0.79-1.41] | [0.74-1.04] | [0.77-.4.27] |
| | | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant |
| Td/IPV + HPV | Never | 1.29 | 0.65 | 0.84 | - | 1.14 | 4.5 | 0.37 | 1.14 | $5.07\times10^{-5}$ |
| | | [0.17-9.51] | [0.09-4.73] | [0.37-1.89] | - | [0.42-3.08] | [0.56-36.15] | [0.05-2.68] | [0.59-2.22] | [$2.64\times10^{-201}$ - $9.72\times10^{191}$] |
| | | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant |

### 5.5.2. Safety of co-administering three vaccines

Vaccine co-administrations increased the RIs (RIR > 1; p<0.05) of fever, rash, gastrointestinal and respiratory events following DTaP/IPV/Hib + MenC + PCV, gastrointestinal events following DTaP/IPV/Hib + MenC + RV, and fever and respiratory events following DTaP/IPV/Hib + PCV + RV, compared to what would have been expected based on the RIs following separate vaccinations (see Table 4). [46] Also the RIs of gastrointestinal and respiratory events following MMR + Hib/MenC + PCV, as well as the RIs of gastrointestinal events and general symptoms following MMR + MenC + PCV were higher than expected following co-administration (see Table 4). [46] There was no or an inhibitory interaction effect of co-administering three vaccines on the RIs of the other AEFI studied (see Table 4). [46]

***Table 4.*** *Relative incidence ratios (RIR) and interaction effects of AEFI for co-administrations of three vaccines. [46]*

| Vaccines co-administered | Recomm. | RIR; [confidence interval]; interaction | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Fever** | **Gastro-intestinal** | **General symptoms** | **Local symptoms** | **Musculo-skeletal** | **Neurological** | **Rash** | **Respiratory / Misc.** | **Sensitivity / Anaphylaxis** |
| DTaP/IPV/Hib + MenB + PCV | Yes | 1.25 | 1.29 | 942.2 | 350.8 | $8.38\times10^{8}$ | $5.31\times10^{4}$ | 0.95 | 1.14 | 0.22 |
| | | [0.80-1.95] | [0.81-2.06] | [$1.65\times10^{-98}$ - $5.39\times10^{103}$] | [0.00-inf] | [0.00-inf] | [$6.13\times10^{-222}$ - $4.60\times10^{230}$] | [0.58-1.54] | [0.86-1.50] | [0.01-4.19] |
| | | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant |
| DTaP/IPV/Hib + MenC + PCV | Yes | 1.93 | 1.31 | 1.25 | 13.87 | $1.53\times10^{5}$ | 1.44 | 1.49 | 1.27 | 1.68 |
| | | [1.63-2.29] | [1.14-1.49] | [0.63-2.51] | [0.74-260.58] | [$2.16\times10^{-121}$ - $1.08\times10^{131}$] | [0.53-3.92] | [1.29-1.74] | [1.17-1.38] | [0.56-5.09] |
| | | Amplifying | Amplifying | non-significant | non-significant | non-significant | non-significant | Amplifying | Amplifying | non-significant |
| DTaP/IPV/Hib + MenC + RV | Yes | 0.94 | 1.65 | 0.7 | $1.74\times10^{7}$ | $1.47\times10^{-5}$ | 1.8 | 1.17 | 1.1 | 1.25 |
| | | [0.69-1.28] | [1.35-2.02] | [0.20-2.38] | [0.00-inf] | [0.00-inf] | [0.20-16.08] | [0.94-1.44] | [0.98-1.24] | [0.11-14.68] |
| | | non-significant | Amplifying | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant |
| DTaP/IPV/Hib + PCV + RV | Yes | 1.44 | 1.16 | 1.31 | $6.29\times10^{-7}$ | $2.43\times10^{4}$ | 0.3 | 1.19 | 1.4 | 0.84 |
| | | [1.09-1.90] | [0.97-1.40] | [0.38-4.46] | [0.00-inf] | [0.00-inf] | [0.03-2.71] | [0.97-1.46] | [1.25-1.57] | [0.07-10.32] |
| | | Amplifying | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | Amplifying | non-significant |
| MMR + Hib/MenC + PCV | Yes | 0.67 | 1.48 | 0.76 | 12.98 | 0.07 | 0.86 | 1.08 | 1.43 | 0.5 |
| | | [0.55-0.80] | [1.20-1.82] | [0.26-2.22] | [0.00-inf] | [0.01-0.41] | [0.36-2.06] | [0.87-1.34] | [1.26-1.63] | [0.20-1.28] |
| | | Inhibitory | Amplifying | non-significant | non-significant | Inhibitory | non-significant | non-significant | Amplifying | non-significant |

| Vaccines co-administered | Recomm. | RIR; [confidence interval]; interaction | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Fever** | **Gastro-intestinal** | **General symptoms** | **Local symptoms** | **Musculo-skeletal** | **Neurological** | **Rash** | **Respiratory / Misc.** | **Sensitivity / Anaphylaxis** |
| DTaP/IPV or dTaP/IPV + MMR + Hib/MenC | Never | 0.80 | 0.65 | 1.11 | - | 0.64 | 0.70 | 1.04 | 1.08 | 0.59 |
| | | [0.37-1.75] | [0.25-1.72] | [0.10-12.89] | - | [0.04-11.67] | [0.06-8.38] | [0.48-2.27] | [0.66-1.76] | [0.03-10.24] |
| | | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant |
| MMR + MenC + PCV | Never | 0.37 | 1.68 | 11.83 | 1.85 | $3.89\times10^{-4}$ | 0.24 | 1.27 | 1.07 | 0.64 |
| | | [0.27-0.51] | [1.07-2.64] | [1.28-109.01] | [0.00-inf] | [$5.81\times10^{-99}$ - $2.6\times10^{91}$] | [0.02-2.37] | [0.83-1.94] | [0.85-1.34] | [0.06-7.46] |
| | | Inhibitory | Amplifying | Amplifying | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant |

### 5.5.3. Safety of co-administering four vaccines

The RIs of the analysed AEFI were not significantly affected by co-administering a fourth vaccine (see Table 5). [46]

***Table 5.*** *Relative incidence ratios (RIR) and interaction effects of AEFI for co-administrations of four vaccines. [46]*

| Vaccines co-administered | Recomm. | RIR; [confidence interval]; interaction | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Fever** | **Gastro-intestinal** | **General symptoms** | **Local symptoms** | **Musculo-skeletal** | **Neurological** | **Rash** | **Respiratory / Misc.** | **Sensitivity / Anaphylaxis** |
| DTaP/IPV/Hib + MenB + MenC + RV | Never | 2.18 | 1.00 | $4.61\times10^{5}$ | - | - | $1.56\times10^{4}$ | 0.65 | 0.57 | $4.24\times10^{4}$ |
| | | [0.42-11.21] | [0.33-3.07] | [$4.06\times10^{-260}$ - $5.23\times10^{270}$] | - | - | [0.00-inf] | [0.24-1.75] | [0.30-1.05] | [0.00-inf] |
| | | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant |
| MMR + MenB + MenC + PCV | Never | 5585 | 2388 | - | - | - | $8.73\times10^{-11}$ | 3029 | - | - |
| | | [$5.71\times10^{-112}$ - $5.47\times10^{118}$] | [$9.26\times10^{-158}$ - $6.16\times10^{163}$] | - | - | - | [0.00-inf] | [$4.53\times10^{-105}$ - $2.02\times10^{111}$] | - | - |
| | | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant | non-significant |

# 6. Discussion

This study evaluated the safety of vaccine co-administrations in children by analysing real-life paediatric immunisation practices in England. It presents unique insights based on a systematic review of the available literature and knowledge in the field, a detailed description of the timeliness of immunisations, an appraisal of scheduled and unscheduled vaccine co-administrations, and a comparative analysis of safety outcomes after co-administering vaccines versus separate immunisation.

## 6.1. Adherence to the paediatric immunisation schedule

The timeliness of routine paediatric immunisations varied across the different vaccines and doses. First doses in the first year of life were administered most often on time, while particularly subsequent doses of a given vaccine and vaccines scheduled after the age of one were not given at the scheduled ages or intervals: first doses were more often given late at older ages and subsequent vaccines too short after a preceding dose. [13] These trends are in line with findings reported in other studies. [21,71–77,87–90] Too short gaps may be due to a delayed preceding dose while the subsequent dose was given at the recommended age. [13] Whereas delayed doses leave children unprotected against vaccine-preventable diseases for an extended time, too short intervals may cause a reduced immune response and an inadequate or less lasting protection. [91] This potentially jeopardises both individual and herd immunity.

Vaccination coverage and timeliness are influenced by complex interactions of multiple factors. [87] We found a small association between increasing area deprivation and lower vaccine schedule adherence [13], which is consistent with findings from previous studies [20,76,88,92]. Since routine paediatric vaccines are covered by the NHS and thus for free, this might be due to other than financial factors related to inadequately using healthcare services as often observed in low income households [93]. Adherence to the immunisation schedule was similar for both genders and differences among the four major English regions were small. [13] This may be explained by the single National Health System all over England, with a homogenous immunisation policy and its implementation, because vaccination timeliness depends on the organisation of the health system and healthcare [94,95]. Nevertheless, vaccinations were generally given on time in the Midlands and East England, while

almost all vaccines were administered less timely in London. [13] This could be related to the heterogeneity in the timeliness of vaccinations across ethnicities in London as reported by others. [88] Others found that vaccination coverage and timeliness tend to improve with vaccine introductions, access to vaccinations and information about them, while vaccine hesitancy – which is determined by contextual factors (socio-cultural, historic, environmental, economic, political, health system related or institutional), concerns related to vaccines, individual perceptions and group influences – causes refusing or delaying vaccinations. [96–99]

We detected two distinct trends following new vaccine introductions in the immunisation schedule. Second and third DTaP/IPV/Hib/HepB doses were given more timely after the vaccine's recent introduction than comparable DTaP/IPV/Hib doses in the years before. [13] This may be due to information campaigns and raised awareness of immunisation schedule updates among healthcare providers, and confirms findings from other studies reporting an improved timeliness when introducing new vaccines [96,97]. We observed that the MenACWY vaccine was mainly given between the age of 14 and 16 or around 18 years. [13] This likely reflects the catch-up programme following the vaccine's introduction in 2016, offering MenACWY vaccine to children who already passed the recommended age of 14 years for MenACWY vaccination. [100]

Our findings underline the importance of addressing both vaccination coverage and timeliness in public health interventions. Such interventions could aim at raising awareness about the importance of timely vaccinations among healthcare professionals and parents through educational, clinical, and policy initiatives [19,73,101–103], as well as strengthening relationships between parents – especially those with a lower socioeconomic status – and healthcare providers [74,104–106], or providing infrastructural support to control the timelines of vaccinations.

## 6.2. Paediatric vaccine co-administration practices

Co-administration practices of routine paediatric vaccines varied between vaccines. Co-administration ratios decreased for vaccines that were scheduled for co-administration later in life, and fewer co-administrations were given as recommended after the first year of life. [3] The majority of vaccine co-administrations were given exactly as recommended or deviated from the actual recommendations by co-administering different doses, fewer vaccines, or co-administering according to an outdated schedule. [3] Some vaccines scheduled to be co-administered were given separately, while a fraction

of routine paediatric vaccines was co-administered as never recommended in any immunisation schedule valid in England during our study period. [3] We observed low co-administration ratios for MenACWY and Td/IPV in our data from GP practices. However, these observations may be unrepresentative for the entire paediatric population because children typically receive those vaccines in schools [100].

Real-life vaccine co-administrations are barely studied by others. One study reported that MenC was co-administered with Tdap in 65% of children, and that 28% of girls received Tdap with HPV in the United States of America. [107] Although these vaccines are not scheduled together in England, these numbers are in line with our findings of suboptimal co-administration practices. [3]

Timely vaccinations were the major determinant for co-administrations as recommended in the immunisations schedule. [3] Particularly delayed vaccinations lead to co-administrations that don't match the recommended schedule. Given that almost 20% of routine paediatric vaccinations are given too late [13], concerted public health action aiming at improving the timeliness of vaccinations would be an appropriate strategy to increase the ratio of recommended co-administrations.

Differences in vaccine co-administration between genders, NHS regions, and IMD quintiles were small, which is consistent with the little influence of these factors on the timeliness of vaccinations. [3,13] Other studies reported that fewer vaccines are preferred by parents to evade potential adverse events or discomfort, rather than being driven by socioeconomic determinants. [108–110] Also clinicians who may avoid vaccine co-administrations due to concerns about a higher risk of undesired effects can be a factor in forsaking co-administrations. [43] Such arguments can be tackled by addressing the safety concerns of both parents and healthcare professionals. [3]

Although deviated vaccine co-administrations (i.e. other doses than recommended, co-administering according to an outdated schedule, or fewer vaccines) indicate that the immunisation schedule is not fully adhered to, the health outcomes are probably barely affected. [3] However, vaccine co-administrations that have not been recommended, particularly when off-label, may result in undesired or unknown efficacy and safety outcomes. [24,25] Alo the beneficial effects of vaccine co-administrations on vaccination coverage [30,33,111], vaccine acceptance [33], and costs [33] aren't fully achieved with suboptimal co-administration ratios. [3] In the light of declining vaccine coverage rates below the targeted 95% for paediatric vaccines [15], promoting co-administration may be a useful strategy to augment coverage. [3]

## 6.3. Safety of paediatric vaccine co-administrations

We found no interaction effects following vaccine co-administration for most (72%) of the AEFI studied, and amplifying effects following co-administration for 11% and inhibitory effects for 17% of the AEFI. [46] These observations correspond largely with the findings from our initial literature review where 16% of studies reported more AEFI and 10% less AEFI following vaccine co-administrations, while the majority of studies found no statistically significant differences. [37] Some studies found statistically significant increases following vaccine co-administration compared to separate vaccinations for injection site bruising, injection site pain, injection site swelling, and myalgia after MenACWY + Tdap + HPV [112–114], pyrexia after DTaP/IPV/Hib/HepB + PCV7 [115], injection site tenderness and headache after Td + MMR + HepB [116], pyrexia after PCV13 + IIV3 [24], vomiting after DTaP/IPV/Hib + MenC + RV [117], and overall adverse events after DTaP/IPV/Hib + MMR [118]. [37] Other studies reported statistically more AEFI following separate vaccinations compared to co-administration for diarrhoea and pyrexia after DTaP/IPV + RV5 [119], injection site erythema after DTaP/IPV/Hib/HepB + MenC [120], rash and rhinorrhea after MMR + VAR + Hib/HepB [121], and nasopharyngitis and insomnia after PCV7 + MMRV [122]. [37] Overall, we detected more differences than reported by others so far, which may be explained by our study design that specifically aimed to evaluate differences in the RI of AEFI between vaccine co-administrations and separate administrations with sufficient statistical power.

Half of 20 vaccine co-administrations had an increased RI for at least one AEFI. [46] Five from seven co-administrations of three vaccines (DTaP/IPV/Hib + MenC + PCV, DTaP/IPV/Hib + MenC + RV, DTaP/IPV/Hib + PCV + RV, MMR + Hib/MenC + PCV, MMR + MenC + PCV) had higher RIs than expected for at least one of these AEFI: fever, rash, general symptoms, gastrointestinal, and respiratory events. [46] Similar increased incidences after co-administering three vaccines were reported in clinical trials: fever and gastrointestinal events following DTaP/IPV/Hib + MenC + PCV [123,124], gastrointestinal events after DTaP/IPV/Hib + MenC + RV [37,117], and fever after DTaP/IPV/Hib + PCV + RV co-administration. [125] The scheduled co-administration of MMR + PCV increased the RIs of fever, rash, and neurological events. One other study found more [126] and another less [127] fever after this co-administration. [37] The unscheduled co-administrations of MMR + MenC caused more fever and DTaP/IPVHib + MMR more musculoskeletal events. Other studies

observed more febrile seizures after MMR + MenC [128] and an overall increase in AEFI after DTaP/IPVHib + MMR [118]. [37]

Co-administering two vaccines led to amplifying interaction effects for AEFI that occurred less following immunisation than in the control period. [46] Despite the increased RIs of these AEFI after co-administration, these events still occurred less than in the control period (RI < 1), indicating a retained but reduced protective effect when co-administering vaccines. [46] We observed this after DTaP/IPV/Hib + MenC for fever and neurological events, and after DTaP/IPV/Hib + RV for fever. [46] Other studies on these two vaccine co-administrations reported no differences between co-administration and separate vaccination. [37,129–131]

Twenty-eight percent of the analysed AEFI after co-administering two vaccines and five percent of analysed AEFI after co-administering three vaccines had a lower RI than would have been expected based on the RIs after separate administration. This inhibitory effect was also reported after DTaP/IPV + RV for diarrhoea and fever [132], DTaP/IPV/Hib/HepB + MenC for erythema [133], and MMRV + PCV for nasopharyngitis and insomnia [134]. [37]

We found no further significant interaction effects after adding a fourth vaccine for the AEFI studied and the two unscheduled co-administrations of four vaccines included in our study haven’t been studied elsewhere yet. [46]

Routine paediatric vaccine co-administrations that were never recommended weren’t less safe than recommended co-administrations according to our analyses of RIRs. Among the analysed co-administrations of two vaccines, two recommended (DTaP/IPV/Hib + PCV, DTaP/IPV or dTaP/IPV + MMR) and four never recommended (DTaP/IPV or dTaP/IPV + Hib/MenC, DTaP/IPV or dTaP/IPV + PCV, MMR + Td/IPV, Td/IPV + HPV) co-administrations showed no increased RI of any AEFI, in line with other studies. [130,135–137] Although one study found more fever, local and general symptoms following DTaP/IPV/Hib + MenB + PCV [138], we didn’t find an increase for any AEFI after this recommended co-administration of three vaccine, nor after the never recommended co-administration of DTaP/IPV or dTaP/IPV + MMR + Hib/MenC. Neither did the never recommended co-administration of a fourth vaccine increase the incidence of AEFI’s and no other studies reported such safety issues. However, never recommended co-administrations are rare and so is the available data on AEFI for such co-administrations, which limits the potential to detect statistically significant differences between separate and co-administrations.

Our findings indicate a safety signal for several AEFI after co-administering three vaccines, as we found previously undetected interaction effects for AEFI after co-administering three vaccines. This signal should be further explored by signal strengthening and signal confirmation studies evaluating the strength of evidence for the signals generated in our study. Such studies must be designed to test hypothesised associations between vaccine co-administrations and AEFI [78] as indicated by our findings, and would benefit from augmenting routine data collection and analysing supplementary data.

## 6.4. Limitations

Real-life data from more than six million vaccinations in children allowed a detailed description of vaccine schedule adherence and co-administration practices in England, as well as an in depth analysis of the safety of routine paediatric vaccine co-administrations. [3,13,46] Observational studies using secondary data analyses from existing datasets are the most feasible option to study the safety of paediatric immunisation schedules [47] and cohort studies are the benchmark study design for evaluating risks associated with vaccines [78] that can be performed retrospectively in health record databases. The large dataset allowed powerful analysis, which is imperative particularly for studying rare AEFI. Despite the strengths associated with this large cohort size, the data in the underlying medical records was entered by various persons at different institutions to document medical practices and not for research purposes. This could introduce unknown confounding by unregistered factors, errors, misclassification, and incompleteness, and overall heterogeneity in the quality of the recorded data. In addition, our analyses were restricted to the variables available in the database. [139] The RCGP RCS database contains data only from GP practices thus the data can be biassed since we do not have vaccination data from other healthcare facilities. However, this effect may be small because routine childhood vaccines in England are mostly given by GPs [140]. Children may have dropped out of the database over the study period and vaccinations received thereafter are not captured. Our analyses were subject to left and right censoring: early vaccinations of children born at the beginning of the study period may have been missed, and late vaccinations that were given after the study period, in particular for children born at the end of the study period, could not be considered. [13]

We could not calculate the exact ages of vaccination for first doses because only the month and year of birth are available to assure the anonymity of children in the database. We used acceptability

windows as described before to deal with this imprecision. This approach leads to higher adherence rates [13] and has consequences for the vaccines scheduled at two months or eight weeks (i.e. first doses of DTaP/IPV/Hib/HepB, DTaP/IPV/Hib, PCV, MenB, and RV): vaccinations that in reality were given within two weeks before the clinically accepted minimum age of six weeks might have been classified as timely. [13] The applied acceptability windows did not include the minimum ages listed in immunisation guidelines for any other vaccines and doses. [28,68,141]

Our risk interval cohort study assessed individuals over an exposed and unexposed period and we used SCCS to analyse differences in relative incidences of AEFIs between separate vaccination and co-administration. This method requires only cases to estimate the RI, which is appropriate for studying vaccinations with high coverage that have few unvaccinated controls, and controls implicitly for fixed confounders. [79,81] On the other hand, absolute incidences cannot be estimated. [79] We could not control for potential confounding factors that are not captured in the database and may differ between children who received separate vaccinations or co-administration. [46] Powerful analyses were possible thanks to the large dataset with real-life vaccination and adverse event information. [46] However, adverse event data may be prone to reporting bias due to parents' different GP consultation behaviours for events occurring after vaccinations compared to when such events would manifest otherwise. [46] Hence, future studies are required to confirm our findings, ideally with other methods using the same data as well as replicating our approach on data from other sources. [46]

# 7. Conclusions

Our study revealed that children are at risk of suboptimal immunisation and protection during specified periods in their childhood due to untimely vaccinations. [13] The currently used measures for coverage neither detect delayed vaccinations less than eight up to 20 months – depending on the vaccine – after the recommended age, nor assess the validity of subsequent doses given at untimely intervals. [13] Hence, we argue for a monitoring tool that includes the timelines of vaccinations. [13] Such a tool should also assist healthcare professionals in assessing the validity of untimely doses, in addition to indicating the completeness of vaccine series. [13] We also recommend using a compound measure combining the timeliness of vaccination with coverage, providing a more precise indication for children's protection against vaccine-preventable diseases. [13] This could be easily done with today's electronic patient data infrastructures capturing exact vaccination ages. Moreover, we advise to address the importance of timely vaccinations in immunisation campaigns. [13]

Timely vaccinations are instrumental for vaccine co-administrations as recommended in the immunisations schedule because delayed vaccinations increase the odds for deviated or never recommended co-administrations, contributing to the reported suboptimal co-administration practices. [3] Consequently, the potential advantages of vaccine co-administrations – e.g. better uptake of vaccines, cost-efficiency – are not fully exploited. Both parents and healthcare providers may benefit from counsel about the benefits of vaccine co-administration to pursue vaccine co-administrations as recommended.

We have demonstrated that co-administrations of two vaccines in real-life are at least equally safe as administering the respective vaccines separately, while adding a third vaccine may increase the relative incidence of AEFI. [46] This points out the importance of monitoring both the incidence and severity of AEFI following vaccine co-administrations specifically, and evaluating whether these risks are outweighed by the benefits of co-administering vaccines, such as fewer GP visits. [46] To this end, we recommend enhanced surveillance aiming at a comprehensive evaluation of the burden of AEFI following vaccine co-administrations. [46]

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