

Summary of evidence on the administration of multiple injectable vaccines in infants during a single visit: safety, immunogenicity, and vaccine administration practices

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Introduction

As new vaccines are introduced into national immunization programmes, there is an increasing need to provide clear and sound guidance to countries on how to handle the administration of multiple injectable vaccines to infants during the same immunization visit. In view of perceived hesitancy of health care workers or caretakers about accepting the administration of multiple injectable vaccines during the same visit, some national programmes are choosing various alternatives: delaying scheduled vaccinations, creating additional visits, administering doses during other visits that are not within the recommended interval between doses, or administering injections via different routes to avoid giving more than one injection in the same limb or visit. Even in the case that national programmes do not alter the schedule, apparent hesitancy by vaccinators to administer multiple injectable vaccines can pose a risk to the success of immunization programmes and may result in parents declining scheduled vaccines.

Prior to PCV being recommended for the routine childhood immunization schedule, there were few examples of EPI programs that required more than 1 vaccine in a visit. However, countries using PCV, pentavalent (DTP-HepB-Hib) and IPV vaccines are now faced with the possibility of administering multiple injectable vaccines in one visit. This issue has become more prominent in the context of the Inactivated Polio Vaccine (IPV) introduction as part of the Polio Eradication and Endgame Strategic Plan 2013-2018. Although many country EPI programmes have been administering two injectable vaccines at a visit (mainly pentavalent and PCV vaccines), the addition of the injectable IPV at 14 weeks can lead to recommendations that three injectable vaccines be administered at a single visit, which has caused concern in some countries. Although there are no specific SAGE recommendations on multiple injections in the context of administering pentavalent, PCV, and IPV in one visit, WHO has provisionally provided the following recommendations:

- IPV (non-adjuvanted) can be given intramuscularly (IM) or subcutaneously (SC), but because of reduced reactogenicity and easier administration, the WHO recommends the IM route.
- For IM injections in infants below 15 months of age, the deltoid injection site (upper arm) should not be used due to its inadequate muscle mass.
- When three IM injections are scheduled simultaneously in children under 15 months of age, it is safe and acceptable to give 2 injections in the same thigh.
- For this, the WHO recommendation is: One thigh: PCV+IPV, separated by 2.5 cm; the other thigh: DTP-HepB-Hib.

We present the evidence from both the peer-reviewed and grey literature that pertains to the recommendations on multiple injections at a single visit. Information in this document focuses on the administration of IPV, PCV, and DTP-HepB-Hib vaccines as these will be the vaccines most commonly

administered simultaneously during the same visit, once all countries have introduced IPV. Acellular-pertussis containing vaccines were not the focus of this summary as they are not often used in developing countries. However, they were included in some of our findings on adverse events following simultaneous administration of vaccinations because the studies provided relevant information for our review when such information was lacking for whole cell pertussis vaccines. We organized our findings based on four topic areas:

1. Biological Issues: Is there evidence that giving immunizations simultaneously at the same visit has the same biologic effect as when they are given alone?
2. Safety Issues: Is it safe to administer multiple injectable vaccines simultaneously? Are there any cumulative enhanced adverse effects from administering multiple injectable vaccines simultaneously?
3. Methods of Administration: What is the recommended method for administering multiple injections in a single visit?
4. Programmatic: What is the recommended practice for preparing for an immunization session at which multiple injectable vaccines will be administered?

Methods

A systematic review was conducted on the administration of multiple injectable vaccines to an infant in a single visit, and articles were reviewed for evidence on each of the following topics:

1. Non-inferiority (immunogenicity and risk of adverse events) of giving two or more injections in the same limb compared to administration in different limbs.
2. Adverse events from administration of multiple injectable vaccines in a single visit.
3. Basis for the recommendation of giving two injections 2.5 cm (1 inch) apart.
4. Suitability of using the deltoid for intramuscular injections in infants.
5. Preference of the intramuscular versus the subcutaneous route of vaccine administration.
6. Recapping procedures and preparation of multiple vaccines for single visit.

Medline (PubMed) and Embase databases were used to search for the terms indicated in Table 1. Articles were compiled in EndNote 7, all duplicate articles were removed.

Table 1. Search terms used for Medline and Embase databases*

Database	Vaccine Types	Search Terms
Medline	<i>Vaccine type terms (type1-12)</i> Polio IPV Pneumococcal PCV Diphtheria Tetanus Pertussis DTP Hepatitis B HepB <i>Haemophilus influenza</i> type b Hib	Anatomic site vaccine Arm administration vaccine Arm injection vaccine Injection site vaccine type1-12 Separate extremities vaccine Separate limbs vaccine Thigh administration vaccine Thigh injection vaccine Vaccination site type1-12 Co-administrated vaccine Co-administration vaccine Coadministrated vaccine Coadministration vaccine Coadministration vaccine type1-12

		Concomitant administered vaccine Concomitant injection vaccine Concomitant vaccine type1-12 Concomitantly administered vaccine Concurrent administration vaccine type1-12 Simultaneous administration vaccine type1-12 Multiple injection vaccine type1-12 Vaccine given in combination type1-12
Embase Searched the following terms, using the limit for human studies, and age groups: infant (up to 1 year), child (unspecified age), preschool child (1 -6 years), school child (7-12 years)	<i>All articles were filtered by type of vaccine in the title and abstract using the following terms:</i> DTP Inactivated polio IPV PCV Pentavalent Pneumococcal conjugate Pneumococcal vaccine Poliomyelitis	Anatomic site vaccine Arm administration vaccine Arm injection vaccine Injection site vaccine Separate limb vaccine Separate extremities vaccine Thigh administration vaccine Thigh injection vaccine Vaccination site Coadministered vaccine Coadministration vaccine Concomitant administration vaccine Concomitant injection vaccine Concomitant vaccine Concomitantly administered vaccine Concurrent administration vaccine Multiple injection vaccine Simultaneous administration vaccine Vaccine given in combination

**Search terms used for each database differed due to the variations in search filters for each database*

Included articles addressed administration to an infant in a single visit via intramuscular or subcutaneous injection of >1 of following vaccines: PCV, IPV, DTP-HepB-Hib. Included articles may also have addressed Japanese encephalitis, measles, rubella, meningococcal conjugate, and yellow fever vaccines. Exclusion criteria for the review were: immunocompromised and non-responding patients, vaccines administered orally or via jet injector, articles without abstracts in English or those that could not be translated, animal studies, and results presented only after a series of vaccinations, rather than after a single visit.

Due to the large number of articles found after the initial search, articles were filtered by exclusion criteria (studies conducted among HIV-infected populations, non-English articles, animal studies, vaccines that were irrelevant to the topics or experimental) and removed from the review. Of the remaining articles, four teams of two individuals reviewed unique sets of articles by title and abstract for inclusion in the full article review. Individuals reviewed titles and abstracts separately and then compared articles that fit the inclusion criteria with his or her team member, discussed any discrepancies, and reached a final consensus on whether an article should be included for full review.

For the review of full articles, 5 individuals each reviewed a unique set of articles and abstracted relevant information using a standardized Excel-based data collection tool. The inclusion and exclusion criteria for the full article review were expanded to include articles presenting data on IPV, DTP-HepB-Hib, and PCV, but excluded articles on acellular pertussis vaccines (see exceptions below for articles addressing each objective) and pain mitigation studies.

Exceptions:

- For articles pertaining to topic 1: include articles comparing data on effects of administering an additional vaccine during a visit (for example, 2 vs. 3 vaccines administered), can include administered vaccine containing acellular pertussis antigen if it is an additional vaccine, but not if it is the initial vaccine given
- For articles pertaining to topic 2: include articles comparing data on effects of administering an additional vaccine during a visit (for example, 2 vs. 3 vaccines administered), can include administered vaccine containing acellular pertussis antigen if it is an additional vaccine, but not if it is the initial vaccine given
- For objectives 3-5: include articles presenting data on 1 or more injections, can include acellular pertussis

After the full article review was completed, articles were excluded if they presented data on the dorsal gluteal as a site of vaccine administration because it is not a recommended site of administration in infants and children due to risk of injury to the sciatic nerve. [1-4] Included articles that pertained to the attitudes of healthcare providers or caregivers on multiple injections were not analyzed as part of this review; these articles were included in the section, “Summary of evidence on the administration of multiple injectable vaccines in infants during a single visit: attitudes of healthcare providers and caregivers”.

Information collected in the Excel-based tool was compiled and synthesized. Results were summarized by objective and categorized into the following groups:

- Evidence of using same limb versus different limbs for multiple vaccines during a single visit
- Safety
- Methods of vaccine administration
- Programmatic issues

Included articles were reviewed for additional relevant references. In addition, individual published and grey literature reviews were conducted for topics 3-6. These individual reviews were supplemented by a review of the WHO vaccine position papers as of February 2015, requests to experts for comments, and data from vaccine package inserts on administration. More details on the methods for the individual reviews can be found in the relevant sections.

Grey Literature Review

In order to supplement the information identified during the systematic review and individual literature reviews, we conducted a grey literature review to identify additional resources that could provide more insight. The following sources were used to identify literature: greylit.org, opengrey.eu, epocoslo.cochrane.org, Google, IRIS, unicef.int, and who.int. Search terms included: simultaneous vaccination, simultaneous immunization, multiple injections, multiple vaccine injections, multiple vaccines, or multiple immunizations. Complete searches using Google, IRIS, and who.int could not be

reviewed in time for inclusion in this report; the first 40-60 search results (which can be considered the most relevant, based on search algorithms) were reviewed, however, only 5 sources were deemed relevant from the initial searches and information from these sources has been included in the summaries of evidence below. The 6th edition of the book *Vaccines*, CDC's Pink Book, and ACIP guidance was reviewed for pertinent information along with any citations that were deemed relevant.

Limitations

We were unable to review all studies that both addressed the objectives and included other types of vaccines in the routine childhood schedule besides PCV, IPV, DTP-HepB-Hib because of time constraints. Many articles and guidance documents included in this review failed to provide data or information that was directly relevant to the objectives of the systematic review. Due to the variety and number of combinations of vaccines administered simultaneously to an infant during a single visit, it was difficult to separate outcomes by type of vaccine. Very few studies addressing the objectives took place in developing countries, and there is no or limited guidance on these objectives from the ministries of health in these countries. The lack of information on the objectives addressed by this review has been noted in other sources; safety and immunogenicity studies often do not report the anatomic site of vaccine administration while frequently documenting the route of administration.[5]

Systematic Review- Overall Results

Figure 1. Number of articles included and excluded in systematic review

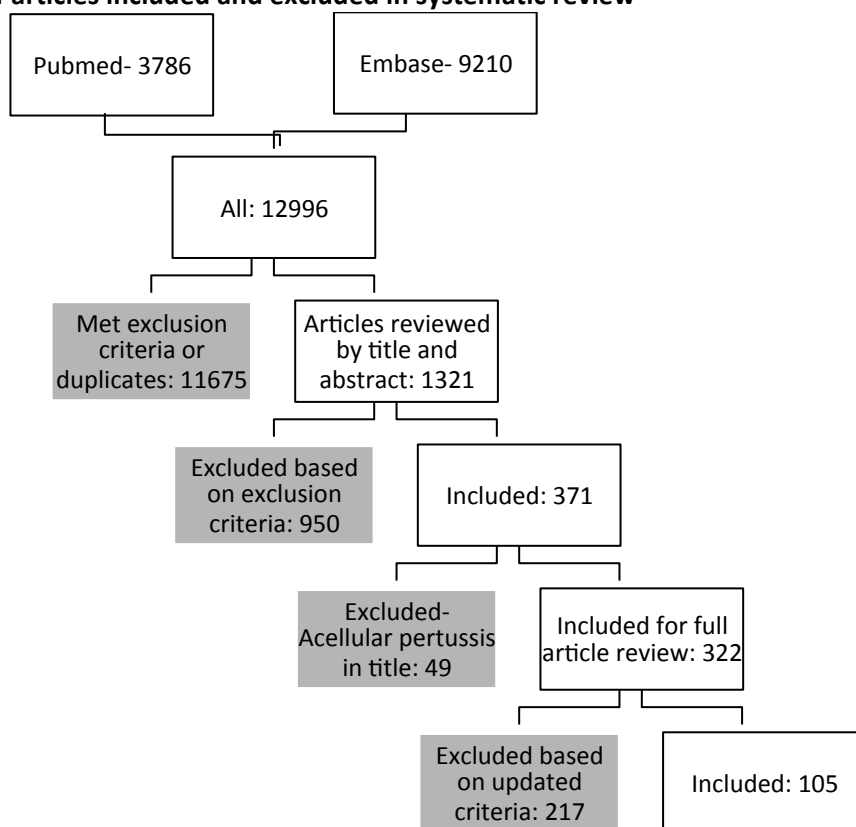


Table 2. Number of articles included after the full review by topic area and region*

Number of Articles	
Topic	
Adverse events	61
Reviews	11
Injection Technique/Prepping for Session/Other	33
WHO Regions	
AFRO	6
EMRO	1
EURO	19
PAHO	49
SEARO	3
WPRO	12
Multiple	3
Not applicable	12
Total	105

*Publication dates ranged from 1985 to 2014.

Summary: Evidence of using same limb versus different limbs for multiple vaccines during a single visit

Addresses topic- 1. Non-inferiority (immunogenicity and adverse events) of giving two or more injections in the same limb compared to administration in different limbs

The systematic review found no studies that evaluated the non-inferiority (immunogenicity and risk of adverse events) of giving two or more injections in the same limb compared to administration in different limbs for infants.

Of note is a recent study from Iro et al. on the effects on immunogenicity of administering PCV13, DTaP-IPV-Hib, and MenC conjugate vaccine to infants in the same limbs for all visits versus alternating the limbs for vaccine injection. As part of that study, the authors conducted a systematic review on the effect of administering vaccines in the same versus different limbs across visits on the immune response to infant vaccination and found no randomized trials. Only one relevant study was identified that took place among adults receiving rabies vaccine. Results from the study suggest that for some antigens in the routine infant immunization schedule, immunogenicity is not reduced, and it may even be improved, by alternating the limb of administration. The authors note that some animal studies have found that draining rather than non-draining lymph nodes have a higher number of antibody-forming cells which may account for differences in immunogenicity by site of vaccination [6-8]. [9]

WHO Recommendations

No direct evidence was identified as the basis one way or the other for the WHO recommendations listed below. Please refer to the “Safety” section for additional evidence on administering multiple injections in one limb.

- When three IM injections are scheduled simultaneously in children under 12 months of age, it is safe and acceptable to give 2 injections in the same thigh.
- For this, the WHO recommendation is: One thigh: PCV+IPV, separated by 2.5 cm; the other thigh: DTP-HepB-Hib.

Summary: Safety

Addresses topic- 2. Adverse events from administration of multiple injectable vaccines in a single visit.

Methods

See “Methods” section above.

Results

Of the 105 articles that met the inclusion and exclusion criteria of the systematic review, 61 (58%) presented data on adverse events following multiple vaccine injections among infants. However, 15 of these articles were later excluded because they included vaccines not relevant to the topics of the systematic review, injection site included the dorsal gluteal site, or results were insufficiently detailed; 45 presented data on adverse events following the administration of multiple injections in the same visit versus separate visits and the addition of another vaccine to a visit for infants. Among the randomized controlled trials, the age of the study population was up through 24 months.

Number of articles presenting adverse event data by vaccine type

Vaccine type	Number of articles
DTP, DTP-containing	17 (excluding DTP-HBV-Hib vaccine)
PCV, PCV-containing	15
DTP-HBV-Hib	6
IPV	5
Other	2
Total	45

PCV

Summary: 15 studies included PCV7, PCV11, PCV13, PCV23, or PCV-DTP-Hib vaccines along with one or more of the following vaccines: DTaP-HepB-IPV-Hib, DTaP-IPV-Hib, DTP, DTP-Hib, DTwP-HepB-Hib, HepB-Hib, HepA, HepB, Hib, MMR, OPV, varicella, or meningococcal conjugate serogroup B (4CMenB). In general, there were no significant differences in the incidence of severe or serious adverse events when a PCV vaccine was given as the additional vaccine in a multiple injection visit vs. when a PCV vaccine was not given or when PCV was administered alone versus with other vaccines [10-23]. However, the frequency of at least one type of minor local or systemic adverse events was sometimes higher in recipients who received a PCV and one or more other vaccines at a single session instead of just the other vaccine(s), although which particular minor local or systemic adverse event was more common varied across studies [13, 14, 17, 20, 21, 23]. In one study, 17 serious adverse events judged to be vaccine related occurred in participants who received DTaP-IPV-HBV-Hib, PCV7, and 4CMenB vaccine while 1 serious adverse event judged to be vaccine related occurred in participants who received only DTaP-IPV-HBV-Hib and PCV7. [24] Although PCV7 was included in the study, any difference in adverse event rates between the two groups was likely related to the 4CMenB vaccine. Of note, one study found that infant immune responses to HepB vaccine and Hib vaccine were significantly reduced and increased, respectively, when the HepB vaccine was administered in the same thigh as DTaP-IPV-Hib and concurrently with PCV7, albeit with PCV7 administered in a different thigh, vs. when the HepB vaccine was administered in a different thigh from DTaP-IPV-Hib and at a different time from PCV7 [15].

IPV

Summary: There were 5 studies identified that included IPV as one vaccination in a multiple injection session. The IPV vaccine was either administered at a separate site or in one of the following

combination products: DTaP-IPV-Hib, DTaP-IPV, or DTP-IPV. Other vaccines studied in the reviewed trials included: DTaP, DTwP, DTaP-HepB, HepB, Hib, meningococcal conjugate, BCG, yellow fever, or MMR. Overall, IPV administered in a combination product or alone was well tolerated by infants in the reviewed studies. [25-29] Two studies among Senegalese infants found no increase in adverse reactions following simultaneous administration of DTP-IPV vaccine with HepB and/or yellow fever, measles, and BCG when compared to single administration of a vaccine or simultaneous administration of non-IPV containing vaccines. [25, 26] Two infants given DTaP, IPV, Hib, PCV7, and HebB were reported to have nonfebrile seizures during a trial comparing separate but concurrent administration of each vaccine to concurrent administration of DTaP-IPV-Hib vaccine with PCV7 and HepB vaccines [27] Among recipients of either a DTaP-IPV combination product or separate administration of DTaP and IPV, large injection site swelling, of at least 50 mm in diameter, was observed; there was a similar incidence of swelling between study groups. [28]

Pentavalent

Summary: We identified 6 studies that included pentavalent vaccine (DTwP-HepB-Hib); 4 of these studies compared the pentavalent vaccine to separate but simultaneous administration of DTwP, HepB, or Hib during a single session. Other vaccines included in the two remaining studies included: measles, OPV, yellow fever, and PCV7. One study compared simultaneous administration of DTwP-HepB-Hib with PCV7 and OPV or only OPV and found no difference in reactogenicity observed among the study groups. [10] Of note, this study did observe more grade 3 swelling at the DTwP-HepB-Hib injection site than at the PCV7 injection site for all study groups. [10] In an observational study among non-randomized infants from Guinea Bissau, it was observed that the administration of pentavalent vaccine simultaneously with measles and yellow fever vaccine was associated with increased mortality. [32] However, SAGE has previously reviewed findings on non-specific effects of vaccines on childhood mortality and concluded that they neither exclude nor confirm the possibility of beneficial or deleterious non-specific immunological effects of the vaccines under study on all-cause mortality and suffer from substantial unresolved methodologic challenges. [33]

DTP

Summary: There were 17 studies identified that included DTP or DTP-HepB, including either whole-cell or acellular pertussis antigens. Other vaccines in the reviewed studies included: DTaP, DTaP-HepB-IPV-Hib, HepB, Hib, varicella, MMR, and OPV. From the articles we reviewed, we found that in general DTP given alone or in a combination product can be safely co-administered with other vaccines [34-39]; however a number of studies did indicate a higher frequency of reported local adverse events and systemic reactions from the DTP/DTP-containing vaccine compared to other vaccines. [11, 40-46] Several studies have found conflicting results on the co-administration of DTP and MMR; one trial found an association between incidents of seizure and receipt of DTP and MMR on the same day or 8 to 14 days after [47] while an analysis of data from the US's Vaccine Adverse Events Reporting System (VAERS) found no increase in serious adverse events, and similar results were found in a clinical trial. [48, 49]

Conclusion

- In general, simultaneous administration of PCV, IPV, pentavalent, and DTP vaccines with other routine vaccines was well tolerated among infants. However there were a few notable combinations of vaccines that resulted in a reported possible increase in adverse events that should not be overlooked and may need further investigation. These include: meningococcal conjugate administered with hexavalent and PCV7 vaccines, pentavalent administered with measles and yellow fever vaccines, and DTP administered with MMR. Due to the variability of the effects of the different combinations of vaccines than can be co-administered in one visit, vaccination schedules should reflect the data on adverse events and immunogenicity of each specific vaccine combination.

Summary: Methods of administration

Addresses topics-

3. Basis for the recommendation of giving two injections 2.5 cm (1 inch) apart.
4. Suitability of using the deltoid for intramuscular injections in infants.
5. Preference of the intramuscular versus the subcutaneous route of vaccine administration.
6. Additional information on IPV administration.

Basis for the recommendation of giving two injections 2.5 cm apart.

Methods

The search terms 'injections 2.5 cm' and 'injections 1 inch' were entered into PubMed for this search. Titles were initially screened for relevance prior to a full review of the text. Multiple injection guidance documents were reviewed from the Department of Health of Australia; the Public Health Agency of Canada; and the Centers for Disease Control and Prevention and the American Academy of Pediatrics in the United States.

Results

388 titles were reviewed and three abstracts reviewed, but none were found to be relevant.

Pubmed Search:

Search terms	Hits	Title/Abstract Screen	Relevant
injections 2.5 cm	324	3	0
injections 1 inch	64	0	0

The guidance documents from Australia, Canada, and the United States recommend a minimum distance of 2.5 cm or 1 inch between injections in the same limb, but we were unable to identify the evidence on which those recommendations may have been based.

Table 3. Summary of findings from guidance documents

Country	Entity	Recommendation
Canada	Public Health Agency of Canada	Use separate limbs if two IM injections are required. If more than two injections in the same limb are required, administer the two injections into the same muscle separated by at least 2.5 cm (1 inch). In cases where there is insufficient deltoid muscle mass, the anterolateral thigh can be used in children to 35 months of age.[50]
Australia	Department of Health	For infants <12 months of age: The suitable sites for this age group are the anterolateral thighs (preferred) and the ventrogluteal areas. For the routine schedule where only two vaccines are required, one can be given in each thigh. When three or four injectable vaccines are to be given at the same visit, the options are: <ul style="list-style-type: none">•two injections in the same anterolateral thigh, separated by at least 2.5 cm; further IM vaccines can be given in this way in the other thigh, or•one injection into each anterolateral thigh and one injection into each ventrogluteal area (only one injection should be given into each ventrogluteal area). [51]
USA	ACIP, CDC	2011: If multiple vaccines are administered at a single visit, administer each preparation at a different anatomic site. For infants and younger children, if more than two vaccines are injected in a single limb, the thigh is the

		<p>preferred site because of the greater muscle mass; the injections should be sufficiently separated (i.e., ≥ 1 inch if possible) so that any local reactions can be differentiated [52]</p> <p>1994: If more than one vaccine preparation is administered or if vaccine and an immune globulin preparation are administered simultaneously, it is preferable to administer each at a different anatomic site. It is also preferable to avoid administering two intramuscular injections in the same limb, especially if DTP is one of the products administered. However, if more than one injection must be administered in a single limb, the thigh is usually the preferred site because of the greater muscle mass; the injections should be sufficiently separated (i.e., 1-2 inches apart) so that any local reactions are unlikely to overlap [53, 54].[55]</p>
USA	HHS/CDC	<p>Multiple Vaccinations - If multiple vaccines are administered at a single visit, administration of each preparation at a different anatomic site is desirable. For infants and younger children, if more than two vaccines are injected in a single limb, the thigh is the preferred site because of the greater muscle mass. For older children and adults, the deltoid muscle can be used for more than one intramuscular injection. The injection sites should be separated by 1 inch or more, if possible, so that any local reactions can be differentiated. Vaccines that are the most reactive (e.g., tetanus-containing and PCV) should be administered in different limbs if possible. Use of combination vaccines can reduce the number of injections.</p> <p>If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td/Tdap and tetanus immune globulin [TIG] or hepatitis B vaccine and hepatitis B immune globulin [HBIG]), separate anatomic sites should be used.</p> <p>The location of all injection sites should be documented in the patient's medical record. Healthcare practices should consider using a vaccination site map so that all persons administering vaccines routinely use the same anatomic site for each different vaccine.[1]</p>
USA	American Academy of Pediatrics	The distance separating the injections is arbitrary but should be at least 1 inch, if possible, so that local reactions are unlikely to overlap.[56]
	WHO WPRO	"First, IPV and PCV injections should be given in one thigh, with injection sites separated by at least 2.5 centimeters. The pentavalent injection should be given in the other thigh."[57]
	WHO GPEI	"When infants need three injections during the same visit, the first two vaccine injections are given in one thigh, with injection sites separated by at least 2 cm. The third injection is given in the other thigh."[58]

Conclusion

The guidance documents consistently recommended that multiple injections administered in the same limb should be separated by at least 2.5 cm (1 inch); no evidence was reported as the basis for this recommendation, but it was indicated that this distance allowed for local reactions to be differentiated by vaccine type.

Suitability of using the deltoid for intramuscular injections in infants.

Due to the specificity of this topic, a separate literature review was undertaken to ensure all accessible materials were assessed comprehensively. The methods and results presented below were supplemented by any other sources identified during the larger systematic review that were deemed relevant.

Methods

The search terms 'intramuscular injection deltoid' and 'IM injection deltoid' were entered into Google scholar and Pub Med for this search. Titles and abstracts were initially reviewed for relevance prior to a full review of the text. Literature reviews were included if they discussed intramuscular (IM) injection sites for infants or children. Primary source articles were included if their research question pertained to the immunogenicity, safety, or acceptability of immunization in different IM sites in infants or children. The references and citing articles of the reviews selected for inclusion were also reviewed for additional relevant sources.

Results

Five literature review articles and 11 clinical trials or observational studies were identified by the search. The literature reviews stated that the deltoid muscle is not well enough developed for IM injections in infants and cautioned that precise identification of the site and adequate muscle mass are crucial to avoid nerve and muscle injury [59-63].

There was agreement among the authors of the reviews that the deltoid is a small site, limiting the potential number of injections that can safely be administered in a given healthcare encounter. The recommendations for the maximum volume that could be injected into the deltoid muscle were inconsistent and ranged from 0.5ml to 2ml in adults ([61, 62, 64]). Two articles reported that 5ml is an appropriate maximum volume in the vastus lateralis [62, 64]. Lesser amounts should be used for children and individuals with underdeveloped or atrophied muscles [61, 62].

There is a lack of consensus in the literature regarding an appropriate age to begin using the deltoid muscle for IM injection. Sources cite ages from 12 to 35 months as suitable ages to start deltoid IM injections [52, 61-63]. One Canadian study compared adverse events following DTP-IPV administration in 18 month old infants at the vastus lateralis and deltoid sites; they found fewer moderate reactions and greater acceptability of the deltoid site; severe pain occurred in 30.5% of the groups injected in the thigh compared with only 8.1% of the group injected in the deltoid; children vaccinated in the thigh had decreased movement of the extremity more often than those injected in the arm; redness and swelling were observed more often after injection in the arm than in the thigh [54]. One study from China administered PCV7 and DTaP simultaneously in the left and right upper deltoids among infants at 3, 4, and 5 months and found that the majority of subjects experienced no induration/swelling or tenderness that interfered with limb movement. However the study group receiving both vaccines simultaneously had slightly more AEs compared to those receiving either vaccine alone in a single visit (52% for simultaneous vaccination versus 47% for PCV7 followed by DTaP 7 days later and 42% for DTaP only) [65]. Another study from China among infants between 2 and 5 months of age receiving Hib found no difference in local reaction rates between the deltoid and vastus lateralis, although incidence of systemic reactions was lower among the group receiving Hib at the vastus lateralis site than in the deltoid after the 3rd dose. [66]

As an alternative to the deltoid for IM injections, authors of the literature reviews recommend the vastus lateralis muscle (anterolateral thigh) for infants as muscle mass is sufficient from birth [59-64]. It is also appropriate for children receiving multiple injectable vaccines [64]. The risk of major injury was reported to be low because this area does not contain major nerves or blood vessels ([59-62, 64]). Another study from Canada on the administration of DTP and Hib among 18 month olds given in the anterolateral thigh in the first half of the study and in the deltoid for the second half found that rates of local reactions were higher when DTP-containing vaccines were given in the deltoid than when they were given in the anterolateral thigh [53].

The ventrogluteal (hip) site has been presented as a suitable alternative to the vastus lateralis for infants and young children and has a low risk of injury [59-62, 67]. Two recent randomized control trials in Brazil and Australia of vaccines administered to the vastus lateralis and ventrogluteal sites in neonates, infants, and young children found little difference in immunogenicity, safety, or acceptability [68-70]. It should be noted that the ventrogluteal site is different from the dorsogluteal site, which is not recommended for vaccination and has a significant risk of injury.

Many of the key sources cited by these literature reviews are nursing textbooks, not peer-reviewed articles. As one article stated “it was found that ‘proper’ procedure was often non-research based and usually contained erroneous and/or out-of-date recommendations regarding the technique.”[71] Indeed, several articles recommend routinely cleaning the skin and aspirating prior to injection, practices WHO recommends against for vaccination, though all five of the literature reviews identified are for general IM injections and may not reflect best practice for vaccinations. Another study noted that guidelines do not always provide recommendations that discuss the specifics of vaccine administration, such as the appropriate route of injection and the most suitable injection sites. [72]

Conclusion

There is inconsistency among sources on the age to begin using the deltoid for IM vaccine administration among infants; however multiple reviews have stated that the deltoid is not well enough developed for IM injection in infants. The vastus lateralis muscle and ventrogluteal site are recommended as alternative sites for IM injections as studies show that there is equal or more tolerability and equal immunogenicity at these sites.

Preference of the intramuscular versus the subcutaneous route of vaccine administration

Due to the specificity of this topic, a separate literature review was undertaken to ensure all accessible materials were assessed comprehensively. The methods and results presented below were supplemented by any other sources identified during the larger systematic review that were deemed relevant.

Methods

PubMed was used to identify articles using the following search strategy: [Subcutaneous] and [vaccine or vaccines] and [administration] and [human]. The vaccine types included: measles, DTP, PCV, pentavalent, IPV, Hib, HPV, HepB, meningococcal conjugate.

Results

Of the 27 articles identified by the search, there were 14 (52%) articles that met the inclusion and exclusion criteria. A 2008 commentary noted that the practice of intramuscular (IM) versus subcutaneous (SC) administration for vaccines has been based on tradition. This commentary summarized evidence on the routes of administration and reported that for studies which present data on these routes, the IM route is preferred over the SC route; studies included aluminum-adjuvanted, live attenuated, and non-adjuvanted/whole cell vaccines and indicated that injection site reactions were more likely with SC administration and that immunogenicity was greater with the IM route for HepA and B vaccines (including non-infant populations)[73]. A systematic review of articles included in the commentary came to the same conclusion [74]. The authors of the review also noted that there are few studies that directly compare the rate of reactions between SC and IM administration. One study cited in the review noted that IPV administered SC caused very few local reactions and that there was no difference in the frequency of local reactions between IM versus SC administration for IPV-containing vaccines [75].

A few studies presented results by a single route of administration. Among infants 2-6 month old, PCV13 was administered SC and was well tolerated and immunogenic [76]. Similarly, no serious or persistent adverse reactions resulted for infants administered Hib-combination vaccines simultaneously with diphtheria vaccines via the SC route [77]. For additional consideration, one study reported that HepB vaccine has been found to be safe and effective among infants receiving 2 micrograms or recombinant vaccine via the intradermal route [78].

Conclusion

In general, these studies found that immunogenicity is non-inferior between the SC versus the IM route for vaccine administration; however, there is more reactogenicity with the SC route (particularly with adjuvanted vaccines). Therefore the IM route is preferred with the SC route being an acceptable alternative.

Additional Information on IPV Administration

IPV may be given SC or IM per manufacturer's information and there are no clinical trials on the relative immunogenicity of one versus the other. However, IPV is frequently administered as a component of a combination vaccine, which has encouraged the administration of IPV via the IM route even when it is administered without other vaccines [79].

IPV Vaccine Package Insert Information on Administration and Adverse Events by Manufacturer

IPOL (IPV) from Sanofi Pasteur:

"The vaccine should be administered IM or SC; licensed for as young as 6 weeks of age. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. Dose is 0.5 mL. From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular pertussis, Hib, or Hep B vaccines used concomitantly with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection. [Unpublished data from Sanofi Pasteur SA, [80, 81]] No data on the immunological interference between IPOL vaccine and MMR were identified by the manufacturer at the time of the insert's publication, October 2012. Based on data provided in the package insert, among US studies with IPOL vaccine, the percentage of detectable antibody for polio types 1,2, and 3 ranges from 97-100%, 100%, and 97-100%, respectively, following 2 doses administered SC versus 99%, 99-100%, and 95-99% following 2 doses administered IM. No information on adverse events was provided by the manufacturer."

IPV Vaccine from Bilthoven Biologicals:

0.5 mL dose. "The vaccine is given SC or IM. Poliomyelitis vaccine can simultaneously be administered with other vaccines on different injection locations."

Poliovac-PFS (IPV) from Serum Institute of India:

"Poliomyelitis Vaccine (Inactivated) is indicated for active immunization of infants (as young as 6 weeks of age), children and adults. Dose is 0.5 mL. Systemic adverse reactions reported in infants receiving IPV concomitantly at separate sites or combined with DTP have been similar to those associated with administration of DTP alone. Local reactions are usually mild and transient in nature. The most frequently reported side effects are reactions at the site of injection: pain, erythema, induration and systemic reactions like moderate transient fever. Other side effects are oedema that can occur within 48 hours and persist for one or two days, lymphadenopathy, hypersensitivity reaction (urticaria, Quinckes oedema) in response to one of the vaccine components. Anaphylactic reactions occur very rarely. The other reactions are moderate and transient arthralgia and myalgia, convulsions, headaches, moderate and transient paresthesia occurring in the two days following vaccination. After preparation of the injection site, immediately administer POLIOVAC PFS intramuscularly or subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In older children and adults POLIOVAC PFS should be administered intramuscularly or subcutaneously in the deltoid area. From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular pertussis,

Hib, or hepatitis B vaccines used concomitantly with Poliomyelitis vaccine (inactivated), no interferences have been observed on the immunological end points accepted for clinical protection.”

Poliorix (IPV) from GSK:

Dose is 0.5 mL. “Poliorix™ is indicated for active immunisation from the age of 2 months against poliomyelitis. Poliorix™ is for deep intramuscular injection. Administration for infants: anterolateral aspect of the thigh; older children and adults: deltoid. No data are available on subcutaneous administration of Poliorix™. It is current practice in vaccination to coadminister different vaccines during the same session. If Poliorix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites. In clinical studies, Poliorix™ has been administered concomitantly with D, T, P, HBV and Hib antigens. IPV can be given safely and effectively at the same time as measles, mumps, rubella, BCG and yellow fever vaccines and vitamin A supplementation.”

IPV Vaccine from Statens Serum Institut:

Dose is 0.5 mL. “The vaccine should be administered intramuscularly or subcutaneously. The age at the first dose should be at least 6 weeks. Between 1 and 10% of the vaccinees can expect to experience side effects, most frequently as reactions on the injection site, fever and general malaise. Local reaction at the injection site in the way of redness, tenderness and swelling can occur within the first 48 hours after injection and last for 1–2 days. The appearance and seriousness of the local reactions is dependent on the injection site and the route of administration. IPV Vaccine SSI can be given at the same time as other live or inactivated vaccines, including vaccines against measles, rubella, mumps, DTP, DT, TT, Td, BCG, hepatitis B, Haemophilus influenzae type b and yellow fever. Simultaneous vaccinations should be given at different injection sites.”

Polprotec (IPV) from Panacea Biotec:

Dose is 0.5 mL. “From 6 weeks of age, POLPROTEC may be administered following the 6, 10, 14-week schedule, as per the recommendations of the Expanded Programme on Immunization of the World Health Organization. Administer POLPROTEC intramuscularly. Lateral aspect of the mid thigh is the preferred site in infants and small children. In older children and adults, it should be administered in deltoid area. POLPROTEC should not be administered into the buttocks due to the varying amount of fatty tissue in this region, nor by the intradermal route, since these methods of administration may induce a weaker immune response. Concomitant administration, of other parenteral vaccines, with separate syringes at separate sites, is not contraindicated. There is no historical data demonstrating interference of antibody response to Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine (Adsorbed) IP used concomitantly with IPV on the immunological endpoints accepted for clinical protection. All systemic symptoms were mild/moderate in intensity. The incidence of each systemic symptom over all doses was similar in the comparator group. All the unsolicited AEs were mild/moderate in intensity.”

WHO Recommendations

Relevant WHO Recommendations:

- IPV (non-adjuvanted) can be given intramuscularly (IM) or subcutaneously (SC) but because of reduced reactogenicity and easier administration, the WHO recommends the IM route.
- For IM injections in infants below 12 months of age, the deltoid injection site (upper arm) should not be used due to its inadequate muscle mass.

Conclusion:

The systematic review found evidence pertaining to the WHO recommendations listed above. The IPV vaccine is licensed for both IM and SC administration; however, only immunogenicity data following 2 doses of the vaccine is provided by the manufacturer and no route-specific safety information is presented. The immunogenicity data following 2 doses is similar for both routes of administration. For other vaccines, studies have repeatedly shown

that IM administration provides equal or greater immunogenicity and fewer local reactions than SC administration, with some slight variations by vaccine type. This supports the WHO's current recommendation of administering IPV via the IM route.

Regarding the use of the deltoid for IM injections among infants, there is inconsistency in the literature on the appropriate age to begin using this muscle for vaccine administration. The ages reported in the literature for use of the deltoid ranged from 12 to 18 months and have been cited in some sources as up to 3 years. Sources indicate that the deltoid muscle is not well enough developed for IM injections in infants and that the anterolateral thigh (vastus lateralis) is recommended for infants as the mass of this muscle in infants is sufficient and the risk of injury is low since there are no major nerves or blood vessels in this area. Additionally, commentaries from clinicians have brought to light that decision-making regarding use of the deltoid for vaccine administration is often not based on published recommendations. Instead, personal judgment is used to make this decision, based on other biological factors and experience [82]. Therefore, while the WHO's recommendation for using the deltoid at 12 months for vaccination is supported by the guidance identified by the review, more evidence is needed that is relevant to the safety and effectiveness of using the deltoid of infants for vaccination.

Summary: Programmatic Issues

Addresses topic- 5: Recapping procedures and preparation of multiple vaccines for single visit.

Due to the specificity of this topic, a separate literature review was undertaken to ensure all accessible materials were assessed comprehensively. The methods and results presented below were supplemented by any other sources identified during the larger systematic review that were deemed relevant.

Methods

Immunization guides from selected national immunization programs and other organizations were included if they were available online in English, Spanish, or French, and included information on the process for preparing multiple injections for a single child (reviewed references listed below). The search for national immunization guidelines was not comprehensive and is not representative of all national immunization programs. Several additional guidelines were reviewed but did not meet the above criteria (i.e. did not discuss process or had been accessed in other ways and are not available online).

Results

With the availability of vaccines that can be given as a third or fourth or fifth injection in a single vaccination visit, the process of preparing syringes for administration can become more complicated. Anecdotally, EPI staff from multiple countries report some countries are recommending a ‘one at a time’ process, where the first indicated vaccine is drawn up and administered to the infant, the second is drawn up and administered to the same infant, etc. This process raised concerns of an increased risk of injury and administration errors.

The Immunization Action Coalition (USA) recommends drawing up all of the vaccines indicated for one infant in a clean designated area, covering each clean needle with its cap, before administering all the indicated vaccines to the infant in quick succession. While recapping ‘dirty’ needles should be absolutely avoided to prevent needle stick injuries, ‘clean’ needles have no risk of blood-borne pathogen exposure for the health worker or the infant. The 2010 document *WHO best practices for injections and related procedures toolkit* recommends this practice, stating “If the dose cannot be administered immediately for any reason, cover the needle with the cap using a one-hand scoop technique”. According to the CDC manual *Epidemiology and Prevention of Vaccine Preventable Diseases*, also known as the CDC Pink Book, the practice of preparing all of the injections for an infant at one time differs from ‘pre-loading’ in that one dose of each indicated vaccine is prepared for a specific child present in the clinic and syringes are not used for storage, as the amount of time between drawing up and administration is still minimal (CDC discourages ‘pre-loading’)[1]. Similarly, the immunization guidelines from Public Health England and the Australian Government Department of Health recommend changing to a clean needle after drawing up the vaccine but before administration of the vaccine. Although not stated, this process also allows all indicated vaccines for a single child to be prepared, with the needles protected, and all of the vaccines to be administered in quick succession.

Overall, many guidelines reviewed did not have clear instructions for a preferred vaccine preparation process. We were unable to identify existing evidence to support one practice over another. An article by L.J. Tan and the SHAPE Vaccine Delivery Working Group similarly indicated that vaccine preparation and administration is an area that has not been critically evaluated and that guidance varies among programs [72].

References

American Academy of Pediatrics:

<http://redbook.solutions.aap.org/chapter.aspx?sectionid=56798089&bookid=886>

Argentina EPI: http://www.msal.gov.ar/images/stories/bes/graficos/0000000451cnt-2013-06_recomendaciones-vacunacion-argentina-2012.pdf

Australian Government Department of Health:

<http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/handbook10-2-2>

Epidemiology and Prevention of Vaccine Preventable Diseases (CDC Pink Book):

http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/D/vacc_admin.pdf

Immunization Action Coalition: http://www.immunize.org/guide/aov06_administer.pdf

Ministry of Health Kenya:

http://www.mchip.net/sites/default/files/mchipfiles/Immunization%20Manual%20for%20Medical%20and%20Nursing%20Students%20_final%20smaller.pdf

Public Health Agency of Canada: <http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-07-eng.php>

Public Health England Green Book:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/147915/Green-Book-Chapter-4.pdf

South Africa EPI: http://www.health-e.org.za/wp-content/uploads/2014/03/Vaccinators_Manual_Final.pdf

WHO: http://whqlibdoc.who.int/publications/2010/9789241599252_eng.pdf

Summary: WHO Vaccine Position Paper Review

Methods

All WHO vaccine positions papers available online at http://www.who.int/immunization/policy/position_papers/en/ as of 20 February 2015 were reviewed for content relating to co-administration of vaccines. In total, 22 position papers were reviewed. Information from the position papers was abstracted onto a standardized data collection form, including the date of position paper publication, the passages (verbatim) advising on co-administration, the page number of the Weekly Epidemiological Record where the information was found, and references cited in the position paper for the information (if any). Where a statement was made specifically as a WHO position on the vaccine, this was also noted. The information on co-administration was further coded into one of five categories:

1. Statements of multiple antigens existing as one combination injection;
2. Guidance that the antigen can be co-administered with other antigens (this may or may not have included advice on safety, reactogenicity and/or immunogenicity);
3. Guidance regarding possible reduced immunogenicity or increased adverse events with co-administration;
4. Guidance on spacing of two injections (e.g. 2.5 cm apart), location (e.g. thigh vs. deltoid), route of administration (e.g. intramuscular vs. subcutaneous) and/or preparation of injections (e.g. no mixing of vaccines in one syringe); or
5. Evidence gaps in the literature.

Results

Diphtheria

No guidance was presented.

***Haemophilus influenzae* type b (Hib)**

"Manufacturers indicate that Hib vaccine can be given safely and effectively at the same time as routine vaccines included in national immunization programmes. [Manufacturers' specifications] There is no conclusive evidence of differences in the immune response to monovalent or combined Hib conjugate vaccines. However, there is some evidence that Hib conjugate vaccine in combination with acellular pertussis (DTaP-Hib) induces a lower antibody response than Hib conjugate in combination with whole cell pertussis (DTwP-Hib) or separately administered DTaP and Hib conjugate vaccines." [83] "If Hib vaccine is given as a separate injection at the same time as other vaccines, it should be administered at a different site. It should not be mixed in the vial or syringe with any other vaccine unless it has been specifically manufactured and licensed for use in this way."

[Manufacturers' specifications]

Hepatitis B

"The immune responses and safety of these combinations of Hepatitis B vaccines are comparable to those observed when the vaccines are administered separately." [84-86]

Pertussis

"None of the combination vaccines for pertussis (wP and aP) have produced adverse events that had not been observed with any of their separate components." [87] "However, there have been concerns that simultaneous exposure to multiple conjugate antigens could result either in enhanced or suppressed immune responses. A Cochrane review in 2009 found that use of the combined vaccines did not result in a significant increase in the incidence of serious adverse events but may cause more frequent minor reactions." [88]

PCV10 and PCV13

"The immunogenicity and reactogenicity of pneumococcal conjugate vaccines (PCV10 and PCV13) have been shown not to be significantly altered when PCVs are given concomitantly with monovalent or combination vaccines against diphtheria, tetanus, pertussis (acellular and whole-cell vaccines), hepatitis B, polio (inactivated and live oral vaccines), Hib, measles, mumps, rubella, varicella, meningococcus serogroup C (conjugate vaccine),

and rotavirus[this reference compares HIV infected to un-infected children].” [89] “When injected at different sites, PCVs can be administered concurrently with any other vaccines in infant immunization programmes.”

PCV23

“Simultaneous administration of PCV23 does not increase adverse events or decrease the antibody response to either vaccine. The vaccine should not be mixed in the same syringe with other vaccines, for example with influenza vaccine, but may be administered at the same time by separate injection in the other arm.”

IPV/OPV

“No clinically relevant interference has been reported when IPV is used in association with licensed diphtheria-tetanus-whole cell pertussis (DTwP)/ diphtheria–tetanus– acellular pertussis (DTaP), Hib, hepatitis B, pneumococcal polysaccharide conjugate or rotavirus vaccines.” [90] “In developing country settings the simultaneous use of OPV and IPV has induced uniformly high antibody responses to all 3 poliovirus types, consistent with the use of multiple doses of poliovirus vaccines.” [91] “IPV and OPV may be administered simultaneously and both can be given together with other vaccines used in national childhood immunization programmes. For rotavirus, interference [with OPV] has been noted after the first dose but not after completion of the full primary series.” [92]

Tetanus

No information on tetanus vaccines regarding the antigen being co-administered with other antigens, possibility of reduced immunogenicity or increased adverse events with co-administration, or guidance on administration.

Conclusions

The WHO vaccine position papers mentioned the use of the following vaccines administered simultaneously with other vaccines in the routine schedule: Hib, wP/aP, PCV10/PCV13, PCV23, and IPV. There was no guidance on tetanus or diphtheria vaccines being co-administered alongside other antigens. No serious safety concerns were mentioned for any of the vaccines where guidance was available on simultaneous administration.

Table 5. Guidance from WHO Vaccine Position Papers by Vaccine Type

	WHO Guidance			
Vaccine (date of position paper)	Antigen exists as a combination vaccine with other antigens	Antigen can be co-administered with other antigens (may or may not include advice on safety/reactogenicity/immunogenicity)	Possible reduced immunogenicity or increased adverse events with co-administration	Guidance on administration
<i>Haemophilus influenzae</i> type b (09/2013)	Hib vaccine is available in a variety of formulations: liquid Hib conjugate vaccine (monovalent), liquid Hib conjugate combined with diphtheria-tetanus-pertussis (DTP) and/ or hepatitis B; Hib conjugate in combination with meningococcal antigens; lyophilized Hib-conjugate with saline diluent (monovalent) and lyophilized Hib-conjugate for use with liquid DTP, or DTP in combination with other antigens – such as inactivated polio vaccine or hepatitis B vaccine.	Manufacturers indicate that Hib vaccine can be given safely and effectively at the same time as routine vaccines included in national immunization programmes. [Manufacturers' specifications]	There is no conclusive evidence of differences in the immune response to monovalent or combined Hib conjugate vaccines (ref). However, there is some evidence that Hib conjugate vaccine in combination with acellular pertussis (DTaP-Hib) induces a lower antibody response than Hib conjugate in combination with whole cell pertussis (DTwP-Hib) or separately administered DTaP and Hib conjugate vaccines. [83]	If Hib vaccine is given as a separate injection at the same time as other vaccines, it should be administered at a different site. It should not be mixed in the vial or syringe with any other vaccine unless it has been specifically manufactured and licensed for use in this way. [Manufacturers' specifications]
Hepatitis B (10/2009)	Hepatitis B vaccine is available as monovalent formulations or in fixed combination with other vaccines, including diphtheria–tetanus–pertussis (DTP), <i>Haemophilus influenzae</i> type b, hepatitis A and inactivated polio.	The immune responses and safety of these combinations of vaccines are comparable to those observed when the vaccines are administered separately.[84-86]		
Pertussis (wP & aP) (10/2010; revised guidance 07/2014)	Most wP vaccines are combined with diphtheria toxoid and tetanus toxoid. Some wP vaccines are also combined with other vaccines routinely administered during infancy, such as <i>Haemophilus influenzae</i> type b (Hib), hepatitis B (HBV) and inactivated poliovirus (IPV). (389) Although aP vaccines are usually administered in combination with diphtheria toxoid and tetanus toxoid, combinations containing aP vaccine may also include other	None of the combination vaccines have produced adverse events that had not been observed with any of their separate components. [87]	However, there have been concerns that simultaneous exposure to multiple conjugate antigens could result either in enhanced or suppressed immune responses. A Cochrane review in 2009 found that use of the combined vaccines did not result in a significant increase in the incidence of serious adverse events but may cause more frequent minor reactions.[88]	

	vaccines routinely administered during infancy, such as Hib, HBV, and IPV.			
Pneumococcus (PCV10 & PCV13) (04/2012)		The immunogenicity and reactogenicity of the involved vaccines have been shown not to be significantly altered when PCVs are given concomitantly with monovalent or combination vaccines against diphtheria, tetanus, pertussis (acellular and whole-cell vaccines), hepatitis B, polio (inactivated and live oral vaccines), Hib, measles, mumps, rubella, varicella, meningococcus serogroup C (conjugate vaccine), and rotavirus. [89] When injected at different sites, PCVs can be administered concurrently with any other vaccines in infant immunization programmes.		
Pneumococcus (PPV23) (10/2008)		Simultaneous administration does not increase adverse events or decrease the antibody response to either vaccine.		The vaccine should not be mixed in the same syringe with other vaccines, for example with influenza vaccine, but may be administered at the same time by separate injection in the other arm.
Polio (OPV & IPV) (02/2014)		OPV is usually administered concurrently with other vaccines including Bacillus Calmette-Guérin (BCG), diphtheria-pertussis- tetanus (DPT), hepatitis B, measles, and Hib, pneumococcal polysaccharide conjugate or rotavirus vaccines, because no interference with regard to effectiveness or adverse events has been observed with these vaccines.[79, 90, 92] No clinically relevant interference has been reported when IPV is used in association with licensed diphtheria-tetanus-whole cell pertussis	For rotavirus, interference has been noted after the first dose but not after completion of the full primary series.	

		(DTwP)/ diphtheria–tetanus– acellular pertussis (DTaP), Hib, hepatitis B, pneumococcal polysaccharide conjugate or rotavirus vaccines. [90] In developing country settings the simultaneous use of OPV and IPV has induced uniformly high antibody responses to all 3 poliovirus types, consistent with the use of multiple doses of poliovirus vaccines. [91] IPV and OPV may be administered simultaneously and both can be given together with other vaccines used in national childhood immunization programmes.		
Tetanus (05/2006)	Tetanus toxoid vaccines are available as single toxoid (TT), combined with diphtheria toxoid (DT) or low-dose diphtheria toxoid (dT) and in combination with diphtheria and pertussis vaccines (DTwP, DTaP, dTaP or dTaP)... Several new combinations containing DTP/DTaP have been marketed, including vaccines against hepatitis B, Haemophilus influenzae type b and poliomyelitis.			

Summary: Expert Comment and Additional Information

Expert Comment

We asked experts in immunology to provide comments on evidence relevant to topics 1, 3, and 4.

1. Non-inferiority (immunogenicity and adverse events) of giving two or more injections in the same limb compared to administration in different limbs.
3. Basis for the recommendation of giving two injections 2.5 cm (1 inch) apart.
4. Recommendation of not using the deltoid for intramuscular injections in infants.

None could refer us to any literature directly addressing topics 1, 3, and 4.

Global and Regional Status of the Number of Injectable Vaccinations

Source: WHO/UNICEF joint reporting form process: national immunization schedules, 2014.

Available at: http://apps.who.int/immunization_monitoring/globalsummary/schedules

Table 4. Number of injectable vaccinations recommended in a single visit for infants and children 0-2 years of age as of 2015

	Global	AFR	AMR	EMR	EUR	SEAR	WPR
# of countries with data	194	47	35	21	53	11	27
# with 2 injectable vaccine visits	159	35	27	20	42	8	26
# with 3 injectable vaccine visits	47	1	13	7	17	1	9
# with 4 injectable vaccine visits	16	0	6	3	4	0	3
# with 5 injectable vaccine visits	5	0	0	0	5	0	0
% with 2 injectable vaccine visits	82%	74%	77%	95%	79%	73%	96%
% with 3 injectable vaccine visits	24%	2%	37%	33%	32%	9%	33%
% with 4 injectable vaccine visits	8%	0%	17%	14%	8%	0%	11%
% with 5 injectable vaccine visits	3%	0%	0%	0%	9%	0%	0%
<i>Average proportion of total visits with:</i>							
1 injectable vaccine	56%	58%	57%	42%	55%	71%	58%
2 injectable vaccines	35%	42%	28%	47%	30%	27%	32%
3 injectable vaccines	6%	1%	11%	7%	9%	2%	8%
4 injectable vaccines	2%	0%	4%	3%	2%	0%	2%
5 injectable vaccines	1%	0%	0%	0%	2%	0%	0%
Median # of visits	6	5	7	6	7	6	6
# with IPV already*	69	1	6	11	41	0	10
% with IPV already*	36%	2%	17%	52%	77%	0%	37%

Countries Planning to Introduce IPV as a 3rd Injection in a Single Visit

Table 5. Countries planning to introduce IPV as a 3rd injection in a single visit by April 2016 by WHO region*

IPV-Vaccine is a third injection	Number of Countries
Don't know	72
AFR Central	8
AFR East and South	1
AFR West	16
Americas	29
Eastern Mediterranean	2
Europe	12
South East Asia	2
Western Pacific	2
No	28
AFR East and South	4
AFR West	1
Eastern Mediterranean	6
South East Asia	9
Western Pacific	8
Yes	26
AFR Central	2
AFR East and South	14
Eastern Mediterranean	4
Western Pacific	6
Total	126

*Updated March 3rd, 2015.

Year of Introduction and Number of Immunogenic Proteins and Polysaccharides Contained in Selected Vaccines

Table 6. Reproduction of Table 76-3 from Vaccines (6th Edition), p. 1471 [79]

Table 76-3 Year of Introduction and Number of Immunogenic Proteins and Polysaccharides Contained in Selected Vaccines		
Vaccine	Year of Introduction	No. of proteins or polysaccharides or both
Smallpox*	1796	196
Rabies	1885	5
Diphtheria [†]	1923	1
Pertussis (whole-cell)*	1926	~3,000
Tetanus [†]	1927	1
Yellow fever	1936	11
Influenza	1945	10
Polio (inactivated) [†]	1955	15
Polio (live attenuated)*	1961	15
Measles [†]	1963	10
Mumps [†]	1967	9
Rubella [†]	1969	5
Hepatitis B [†]	1981	1
H. influenzae type b (conjugate) [†]	1990	2
Pertussis (acellular)	1991	2-5
Hepatitis A [†]	1995	4
Varicella [†]	1995	69
Pneumococcus (conjugate)*	2000	14
Meningococcus (conjugate)*	2005	5
Rotavirus [†]	2006	11-16
Human papillomavirus [†]	2006	2-4

*Formerly in the US routine child and adolescent immunization schedule

[†]Currently in the US routine child and adolescent immunization schedule

Key Conclusions

Key Conclusions and Recommendations:

- IPV (non-adjuvanted) can be safely and effectively given intramuscularly (IM) or subcutaneously (SC). However, the IM route is generally less reactogenic for inactivated vaccines. When IPV is administered as part of a combination vaccine, the route of administration should also reflect the optimal route for the other antigens in the combination vaccine.
- Intramuscular injection sites should be chosen to minimize the risk of nerve and muscle injury from the act of inserting a needle into the muscle and to maximize the probability of an adequate immune response. Systematic comparisons of the risks and benefits of different possible intramuscular injection sites for infants are lacking, but the vastus lateralis (thigh) muscle is a viable site with the ventrogluteal (hip) muscle as an acceptable alternative. The deltoid (upper arm) muscle is another viable site for children, with 12 through 18 months being common ages for the initiation of the use of this site. However, the use of the deltoid may need to be delayed if the muscle is atrophied. The dorsogluteal site (buttock) is not recommended due to the high risk of injury.
- The schedule used for vaccinating children should maximize the likelihood that the children will be fully protected against vaccine preventable diseases while minimizing the risks of vaccine adverse events. For infants, administering the DTP-Hepatitis B-Hib vaccine, IPV, and a PCV at the same visit, all intramuscularly, is a viable option for achieving these goals. Systematic comparisons of the risks and benefits of the various possible sites for administering infants DTP-Hepatitis B-Hib vaccine, IPV, and a PCV at the same visit are lacking, but injecting DTP-Hepatitis B-Hib vaccine in one thigh and IPV and PCV in another thigh can be done safely and effectively.
- If two vaccines are injected into the same muscle, they should ideally be spaced far enough apart to allow any localized adverse events they cause to be distinguished. Systematic studies of the best distance for separating vaccine injections are lacking, although a 2.5 cm distance between injections to the vastus lateralis (thigh) or deltoid is a viable option.
- If multiple injectable vaccines are administered in a single visit, care must be taken in the drawing up and preparation of each vaccine. Drawing up all of the vaccines needed for an infant in a clean designated area, covering each clean needle with its cap using a one-hand scoop technique, and then administering of the indicated vaccines to the infant in quick succession is a viable approach. Needles should not be recapped after being used for an injection.
- Countries introducing new vaccines which will increase the number of injections per immunization visit should be strongly encouraged to:
 - Ensure healthcare providers receive information that the safety and biologic effects of providing all recommended vaccines in single visits are generally similar to those of providing them in separate visits, as well as training on communication techniques with parents who may have concerns about the child receiving multiple vaccine injections in a single visit.
 - Develop national vaccination schedules that include multiple vaccine injections in a single visit unless specific evidence exists that doing so will have negative repercussions which outweigh the benefits of administering multiple vaccines in a single visit. Administering multiple injectable vaccines in a single visit may lower costs to the health care system and vaccine recipients and reduce drop-out rates.
 - Monitor the acceptance and effects of simultaneous administration of injectable vaccines per their national vaccination schedule recommendations as a means to identify if any short or long-term problems result from recommending the simultaneous administration of injectable vaccines.
- Due to the variability of the effects of the different combinations of vaccines than can be co-administered in one visit, vaccination schedules should adapt to new data on the adverse events and immunogenicity of specific vaccine combinations as they become available.

Annex

Excerpts from Published Guidance and Recommendations

Table 4. Recommendations by Committee

Committee	Country	Guidance/Recommendations
General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP)[52]	USA	<p>Takes a flexible approach to vaccine administration for multiple injections</p> <p>Simultaneous Administration, p.6</p> <p>“Simultaneous administration of vaccines is defined as administering more than one vaccine on the same clinic day, at different anatomic sites, and not combined in the same syringe. Experimental evidence and extensive clinical experience provide the scientific basis for administering vaccines simultaneously.”</p> <p>“With some exceptions, simultaneously administering the most widely used live and inactivated vaccines has produced seroconversion rates and rates for adverse reactions similar to those observed when the vaccines are administered separately [49, 93-95]. Routine administration of all age-appropriate doses of vaccines simultaneously is recommended for children for whom no specific contraindications exist at the time of the visit. MMR and varicella vaccine can be administered simultaneously.”</p> <p>“Depending on which vaccines are administered during the first year of life, a child might receive up to nine injections at the 12- through 15-month visit (MMR, varicella, Hib, pneumococcal conjugate vaccine [PCV], pediatric diphtheria and tetanus toxoids and acellular pertussis [DTaP], inactivated poliovirus [IPV], hepatitis A, hepatitis B, and influenza vaccines). Although there is no exact limit on the number of injections, with a little flexibility, a provider can ensure that the primary series doses are given without administering too many injections at each visit. To reduce the number of injections at the 12- through 15-month visit, the hepatitis B series and 3 doses of IPV (20) can be administered before the child's first birthday.”</p> <p>“There are many other examples of ways the vaccination schedule provides flexibility.” “The minimum age for administration of combination vaccines is the oldest minimum age for any of the individual components; the minimum interval between doses is equal to the greatest minimum interval of any of the individual components. With use of the combination Hib-hepatitis B vaccine, the minimum age of administration of the final dose is 12 months because of the minimum age requirement for the last dose of the Hib series (26).”</p> <p>Non-simultaneous Administration, p. 8</p> <p>“There is no evidence that inactivated vaccines interfere with the immune response to other inactivated vaccines or to live vaccines. Any inactivated vaccine can be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine (Table 3). Limited data are available regarding interference between live vaccines used in the United States. The immune response to one live-virus vaccine might be impaired if administered within 28 days (i.e., 4 weeks) of another live-virus vaccine (52,</p>

		<p>53)."</p> <p>Route of Administration, p. 14</p> <p>Intramuscular Injections</p> <p>Infants (Aged <12 months)</p> <p>For the majority of infants, the anterolateral aspect of the thigh is the recommended site for injection because it provides a large muscle mass (Figure 2). In certain circumstances (e.g., physical obstruction to other sites and no reasonable indication to defer doses), the gluteal muscle can be used. If the gluteal muscle must be used, care should be taken to define the anatomic landmarks.¶¶ Injection technique is the most important parameter to ensure efficient intramuscular vaccine delivery. If the subcutaneous and muscle tissue are bunched to minimize the chance of striking bone (95), a 1-inch needle is required to ensure intramuscular administration in infants aged ≥1 month. For the majority of infants, a 1-inch, 22- to 25-gauge needle is sufficient to penetrate the thigh muscle. For neonates (first 28 days of life) and preterm infants, a ⅝-inch needle usually is adequate if the skin is stretched flat between the thumb and forefinger and the needle is inserted at a 90-degree angle to the skin (97).</p> <p>Toddlers (Aged 12 Months- 2 Years)</p> <p>For toddlers, the anterolateral thigh muscle is preferred, and if used, the needle should be at least 1 inch long. The deltoid muscle can be used if the muscle mass is adequate. A ⅝-inch needle is adequate only for the deltoid muscle and only if the skin is stretched flat between thumb and forefinger and the needle is inserted at a 90-degree angle to the skin.</p> <p>Children (Aged 3-18 Years)</p> <p>The deltoid muscle is preferred for children aged 3--18 years (Figure 3); the needle size for deltoid site injections can range from 22 to 25 gauge and from ⅝ to 1 inch on the basis of technique. Knowledge of body mass can be useful for estimating the appropriate needle length (99); however, neither a physical examination nor measurement of body mass is necessary to administer vaccines. Most children in this age range require a ⅝- or 1-inch needle (or intermediate size, if available).</p> <p>Multiple Injections</p> <p>If multiple vaccines are administered at a single visit, administer each preparation at a different anatomic site. For infants and younger children, if more than two vaccines are injected in a single limb, the thigh is the preferred site because of the greater muscle mass; the injections should be sufficiently separated (i.e., ≥1 inch if possible) so that any local reactions can be differentiated (92,100). For older children and adults, the deltoid muscle can be used for more than one intramuscular injection. If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td/Tdap and tetanus immune globulin [TIG], hepatitis B and hepatitis B immunoglobulin [HBIG]), separate anatomic sites (i.e., different limbs) should be used for each injection. The location of all injection sites should be documented in the patient's medical record. Health-care practices should consider using a vaccination site map so that all persons administering vaccines routinely use a particular anatomic site for each different vaccine.</p>
American		"Simultaneous administration of most vaccines is safe, effective and

<p>Academy of Pediatrics – Report of the Committee on Infectious Diseases (Red Book): Simultaneous Administration of Multiple Vaccines 2012 [96]</p>		<p>recommended. Infants and children have sufficient immunologic capacity to respond to multiple vaccines. No contraindications to the simultaneous administration of multiple vaccines routinely recommended for infants and children are known. Immune response to one vaccine generally does not interfere with responses to other vaccines. Simultaneous administration of IPV, MMR, varicella, or DTaP vaccines results in rates of seroconversion and of adverse effects similar to those observed when the vaccines are administered at separate visits. MMRV is associated with a higher rate of fever and febrile seizures after the recommended first dose than MMR and varicella administered separately at the same visit. Because simultaneous administration of routinely recommended vaccines is not known to affect the effectiveness or safety of any of the recommended childhood vaccines, simultaneous administration of all vaccines that are appropriate for the age and immunization status of the recipient is recommended. [52] When vaccines are administered simultaneously, separate syringes and separate sites should be used, and injections into the same extremity should be separated by at least 1 inch so that any local reactions can be differentiated. Simultaneous administration of multiple vaccines can increase immunization rates significantly. Some vaccines administered simultaneously may be more reactogenic than others (see disease-specific chapters). Individual vaccines should never be mixed in the same syringe unless they are specifically licensed and labeled for administration in one syringe. If an inactivated vaccine and an immune globulin product are indicated concurrently (eg, hepatitis B vaccine and HBIG, rabies vaccine and RIG), they should be administered at separate anatomic sites.”</p>
<p>Public Health Agency of Canada, 2013 [50]</p>	<p>Canada</p>	<p><i>Subcutaneous (SC) injections</i> For infants younger than 12 months of age, the usual site for SC administration of vaccine is the subcutaneous tissue of the anterolateral thigh; if necessary, the upper triceps area of the arm may be used. SC injections for vaccine recipients 12 months of age and older are usually given into the subcutaneous tissue of the upper triceps area of the arm. SC injections should be administered at a 45° angle.</p> <p><i>Intramuscular (IM) injections</i> IM injections of vaccine are administered at a 90° angle into the vastus lateralis muscle (anterolateral thigh) in infants less than 12 months of age and into the deltoid muscle of persons 12 months of age and older (unless the muscle mass is not adequate, in which case the anterolateral thigh can be used). For the injection of diphtheria, tetanus, acellular pertussis (DTaP) vaccine in children 12 to 35 months of age, the deltoid muscle or anterolateral thigh can be used. A large retrospective cohort study of children 12 to 35 months of age demonstrated a lower risk of medically- attended local reactions when DTaP vaccine was given into the thigh compared to vaccination into the arm.</p> <p>Appropriate site selection is important to avoid inadvertent injection into a blood vessel or injury to a nerve. Vaccines containing adjuvants must be injected intramuscularly. If a vaccines containing an adjuvant is inadvertently injected subcutaneously or intradermally, increased inflammation, induration or granuloma formation may occur. Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional information about IM administration</p>

		<p>of vaccines to people with bleeding disorders.</p> <p>Active immunizing agents should not be administered into the buttock (gluteal muscle). Immunogenicity is lower to hepatitis B and rabies vaccines if given in the buttock, probably because of injection into adipose tissue where the vaccine is not well absorbed. The buttock is an acceptable site for administration of immune globulin when large volumes are administered, and activation of the immune system is not required, but appropriate site selection of the gluteal muscle is necessary to avoid injury to the sciatic nerve.</p> <p><i>Multiple injections</i></p> <p>All opportunities to immunize should be used and giving multiple vaccines at the same clinic visit is encouraged. Giving multiple injections at one visit helps to ensure that individuals are up to date with the vaccines required for their age and risk factors. Generally, infants and children have similar immune responses whether vaccines are given at the same time or at different visits. Although children are now receiving more vaccines, they are exposed to fewer antigenic proteins in today's vaccines than in the vaccines used in the past, because of changes in the vaccine products.</p> <p>Practice considerations for multiple injections include the following:</p> <ul style="list-style-type: none"> - Label syringes to identify which vaccine each syringe contains. - Record the site of administration of each vaccine, so that if an injection site reaction occurs, the associated vaccine can be identified. - Use separate limbs if two IM injections are required. If more than two injections in the same limb are required, administer the two injections into the same muscle, separated by at least 2.5 cm (1 inch). In cases where there is insufficient deltoid muscle mass, the anterolateral thigh can be used. - Administer vaccines that are known to cause more stinging or pain after other vaccines (e.g., Prevnar®13; M-M-R®II, human papillomavirus vaccines [HPV]). - If a vaccine and an immune globulin preparation are administered simultaneously (e.g., tetanus toxoid-containing vaccine and tetanus immune globulin), use separate anatomic sites (different limbs) for each injection.
The Australian Immunisation Handbook, 2013 [51]	Australia	<p>Vaccines administered IM or SC</p> <p>Influenza vaccine[†]</p> <p>Measles-mumps- rubella vaccine (MMR) (Priorix only)</p> <p>Measles-mumps-rubella-varicella vaccine (MMRV) (Priorix-tetra only)</p> <p>23-valent pneumococcal polysaccharide vaccine (23vPPV)[†]</p> <p>Rabies vaccine (HDCV)</p> <p>Yellow fever vaccine</p> <p>[*] IPV-containing combination vaccines are administered by IM injection; IPV (IPOL) is administered by SC injection.</p> <p>2.2.9 Administering multiple vaccine injections at the same visit</p>

		<p>When sequentially administering multiple vaccines to children, give the most painful vaccine last (e.g. pneumococcal conjugate vaccine). Evidence suggests that this may decrease the overall pain response.</p> <p>The location of each separate injection given should be recorded, so that if a local adverse event occurs, the implicated vaccine(s) can be identified.</p> <p>Infants <12 months of age</p> <p>The vastus lateralis muscle in the anterolateral thigh is the recommended site for IM vaccination in infants <12 months of age, due to its larger muscle size.</p> <p>The suitable sites for this age group are the anterolateral thighs (preferred) and the ventrogluteal areas. For the routine schedule where only two vaccines are required, one can be given in each thigh.</p> <p>When three or four injectable vaccines are to be given at the same visit, the options are:</p> <ul style="list-style-type: none"> - two injections in the same anterolateral thigh, separated by at least 2.5 cm (see Figure 2.2.10, injection numbers 1 and 2); further IM vaccines can be given in this way in the other thigh (injection number 3), or - one injection into each anterolateral thigh and one injection into each ventrogluteal area (only one injection should be given into each ventrogluteal area).
Public Health England – Immunisation Against Infectious Disease, 2013 [97]	England	<p>The anterolateral aspect of the thigh is the preferred site for infants under one year old, because it provides a large muscle mass into which vaccines can be safely injected.</p> <p>Where two or more injections need to be administered at the same time, they should be given at separate sites, preferably in a different limb. If more than one injection is to be given in the same limb, they should be administered at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each injection is given should be noted in the individual's records.</p>
General Immunization Practices in <i>Vaccines</i> 6 th Ed. [98]	N/A	<p>"Unless specifically licensed for injection in the same syringe, different vaccines administered simultaneously should be injected separately and at different anatomic sites. If both upper and lower limbs must be used for simultaneous administration of different vaccines, the anterolateral thigh is often chosen for intramuscular injections and the triceps region for subcutaneous injections. If more than one injection must be administered in a single limb of an infant or young child, the thigh usually is preferred because of its large muscle mass. The distance separating two injections in the same limb should be sufficient (eg, 1 to 2 inches) to minimize the chance of overlapping local reactions.^{5, 12, 13} In general, different vaccines, including live virus products, can be administered simultaneously without reducing their safety and effectiveness⁶² (Table 8-4). Studies of cortisol concentration and behavioral responses to vaccination indicate that responses are similar in infants who receive two injections during one visit and infants who receive a single injection, suggesting that a second injection does not increase stress.^{63, 64}</p> <p>Increased severity or incidence of adverse reactions has not been observed after simultaneous administration of the most widely used vaccines.⁵ Similarly, simultaneous administration of vaccines generally does not cause immunologic interference except possibly between pneumococcal conjugate</p>

		vaccine and Menactra brand meningococcal conjugate vaccine.” ^{62, 64}
American Academy of Pediatrics – Report of the Committee on Infectious Diseases (Red Book): Site and Route of Immunization (Active and Passive) (2012) [99]		<p>“For IM injections, the choice of site is based on the volume of the injected material and the size of the muscle, and the needle should be directed at a 90° angle. In children younger than 1 year of age (ie, infants), the anterolateral aspect of the thigh provides the largest muscle and is the preferred site. In older children, the deltoid muscle usually is large enough for IM injection.”</p> <p>“When multiple vaccines are administered, separate sites ordinarily should be used if possible, especially if one of the vaccines contains DTaP. When necessary, 2 or more vaccines can be given in the same limb at a single visit. The anterolateral aspect of the thigh is the preferred site for multiple simultaneous IM injections because of its greater muscle mass. The distance separating the injections is arbitrary but should be at least 1 inch, if possible, so that local reactions are unlikely to overlap.”</p>
Centers for Disease Control and Prevention – Epidemiology and Prevention of Vaccine-Preventable Diseases [100]	USA	<p>General recommendations on Immunization Chapter: “Simultaneous administration (that is, administration on the same day) of the most widely used live and inactivated vaccines does not result in decreased antibody responses or increased rates of adverse reaction. Simultaneous administration of all vaccines for which a child is eligible is very important in childhood vaccination programs because it increases the probability that a child will be fully immunized at the appropriate age. A study during a measles outbreak in the early 1990s showed that about one-third of measles cases in unvaccinated but vaccine-eligible preschool children could have been prevented if MMR had been administered at the same visit when another vaccine was given.</p> <p>All indicated vaccines should be administered at the same visit. There is one exception to this rule. In children with functional or anatomic asplenia pneumococcal conjugate vaccine (PCV) and Menactra brand meningococcal conjugate vaccine should not be administered at the same visit, and should be separated by at least 4 weeks. This is because children with functional or anatomic asplenia are at very high risk of pneumococcal invasive disease and Menactra is thought to interfere with the antibody response to PCV. Individual vaccines should not be mixed in the same syringe unless they are licensed for mixing by the Food and Drug Administration. Only the sanofi-pasteur DTaP-IPV/ Hib (Pentacel) vaccine is licensed for mixing in the same syringe. See Appendix D for additional guidelines for vaccine administration.</p> <p>Combination vaccines are generally preferred over simultaneous administration of single component vaccines. Considerations should include an assessment of the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and costs. Considerations should also include patient choice and the potential for adverse events. For the first dose of vaccine to prevent measles, mumps, rubella and varicella, unless the parent or caregiver expresses a preference for MMRV vaccine, separate MMR and Varicella vaccines should be administered for children 12 through 47 months of age.”</p> <p>Appendix: Vaccine Administration Guidelines: “If multiple vaccines are</p>

		<p>administered at a single visit, administration of each preparation at a different anatomic site is desirable. For infants and younger children, if more than two vaccines are injected in a single limb, the thigh is the preferred site because of the greater muscle mass. For older children and adults, the deltoid muscle can be used for more than one intramuscular injection. The injection sites should be separated by 1 inch or more, if possible, so that any local reactions can be differentiated. Vaccines that are the most reactive (e.g., tetanus-containing and PCV) should be administered in different limbs if possible. Use of combination vaccines can reduce the number of injections.”</p>
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