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# Investigation of an increase in large local reactions following vaccine schedule change to include DTaP-HB-IPV-Hib (Infanrix-hexa®) and MMRV (ProQuad®) at 18 months of age

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ABSTRACT

*Context:* In 2015 in Quebec, Canada, the passive vaccine adverse event reporting system detected an increase in large local reactions associated with vaccines recommended at the 18-month visit. This followed changes to the pediatric vaccine schedule to include hexavalent diphtheria-tetanus-acellular-pertusis-inactivated polio-*Haemophilus influenzae* type b-hepatitis B vaccine (DTaP-IPV-Hib-HB, Infanrix-hexa®, GSK) and quadrivalent measles-mumps-rubella-varicella vaccine (MMRV, ProQuad®, Merck) as 18-month booster doses.

*Objectives:* To determine if the excess of large local reactions was caused by a specific vaccine or their co-administration in the same limb or during the same visit.

*Methods:* A case-control study was conducted among cases born between January 2012 and April 2015 with a large local reaction following MMR ± V or DTaP-IPV-Hib ± HB vaccines administered between 16 and 23 months of age. Controls were randomly selected from the provincial medicare database among children born during the same period.

*Results:* Our analysis included 96 cases and 494 controls vaccinated with MMRV or DTaP-IPV-Hib ± HB vaccines. Among the 96 cases, 46% had a cellulitis and 54% had an injection site reaction extending beyond the nearest joint and/or lasting ≥ 4 days. Among the 39 cases who were immunized in different limbs, 77% of the large local reactions were located at the Infanrix-hexa® site, 5% at the DTaP-IPV-Hib site and 18% at the ProQuad® site. Large local reactions were significantly more frequent with Infanrix-hexa® than with DTaP-IPV-Hib vaccine (OR 5.9 95% CI: 1.4–25.7). Administration of ProQuad® and Infanrix-hexa® in the same limb did not increase the risk of large local reactions.

*Conclusion:* This investigation suggested that most large local reactions were causally associated with the Infanrix-hexa® vaccine and that the risk was not greater when ProQuad® and Infanrix-hexa® were administered in the same limb. Given the improved vaccine coverage for hepatitis B, benefit-risk analysis likely still favours ongoing use of Infanrix-hexa® with informed parental consent.



*Abbreviations:* AEFI, adverse event following immunization; DTaP-IPV, diphtheria toxoid, tetanus toxoid, acellular pertussis and inactivated polio vaccine, regardless of brand; DTaP-IPV-Hib, diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated polio and *Haemophilus influenzae* type b vaccine, regardless of brand; DTaP-HB-IPV-Hib, diphtheria toxoid, tetanus toxoid, acellular pertussis, Hepatitis B, inactivated polio and *Haemophilus influenzae* type b vaccine, regardless of brand; Infanrix-IPV-Hib®, diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated polio and *Haemophilus influenzae* type b vaccine manufactured by GlaxoSmithKline; Infanrix-hexa®, diphtheria toxoid, tetanus toxoid, acellular pertussis, HB, inactivated polio and *Haemophilus influenzae* type b vaccine manufactured by GlaxoSmithKline; LLR, large local reactions; MMR, measles, mumps and rubella vaccine, regardless of brand; MMRV, measles, mumps, rubella and varicella vaccine, regardless of brand; ProQuad®, measles, mumps, rubella and varicella vaccine manufactured by Merck; Priorix-Tetra®, measles, mumps, rubella and varicella vaccine manufactured by GlaxoSmithKline; SI-PMI, Quebec immunization registry; QVAERS, Quebec's vaccine adverse event reporting system.

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## 1. Introduction

In 2015 in Quebec, Canada, the passive vaccine adverse event reporting system (QVAERS) detected an increase in large local reactions (LLR) associated with vaccines recommended at the 18-month visit. There were 53 LLR cases reported in 2015 compared to an annual mean of 16 cases from 2010 to 2014 corresponding to 62.5/100 000 and 19.0/100 000 vaccinees respectively. Medically attended LLRs were also more frequent in 2015 compared to 2010–2014 (47.5/100 000 versus 14.7/100 000 vaccinees respectively).

At the 18-month visit children in Quebec are administered the 2nd dose of the combined measles-mumps-rubella vaccine (1st dose at 12 months) and the 4th dose of the combined diphtheria-tetanus-acellular pertussis-inactivated polio-*Haemophilus influenzae* type b (DTaP-IPV-Hib) vaccine. This increase in LLR occurred in the context of recent changes in both products given at this visit (Table 1). In October 2014, the pentavalent DTaP-IPV-Hib from GSK (Infanrix-IPV-Hib®) was replaced by the hexavalent DTaP-HB-IPV-Hib (Infanrix-hexa®) from the same manufacturer. This hexavalent vaccine had been previously introduced in June 2013 to immunize infants born since April 1, 2013 with three doses given at 2, 4 and 18 months of age. At 6 months, infants still receive a dose of pentavalent vaccine (DTaP-IPV-Hib). In October 2014, the first infants of the cohort immunized with Infanrix-hexa® at 2 and 4 months of age reached 18 months of age. In January 2015, the Merck quadrivalent measles-mumps-rubella-varicella vaccine (MMRV; Proquad®) replaced the quadrivalent version from GSK (Priorix-Tetra®) that had been used since May 2013 in children 18 months of age.

Quebec was the only Canadian province to observe this excess in LLR but also the only province to recommend Proquad® and Infanrix-hexa® at the 18-month visit, whereas other Canadian provinces recommended the pentavalent DTaP-IPV-Hib with or without MMRV at this visit. As a large proportion of patients with LLR in 2015 had received both vaccines in the same limb, the Quebec Ministry of Health legally mandated an epidemiologic investigation to determine if the LLR excess was caused by a specific vaccine (ProQuad® or Infanrix-hexa®), or their co-administration in the same limb or during the same visit. Nine hypotheses were evaluated during this investigation (Table 2).

**Table 1**
Changes in products administered at the 18-month visit between 2012 and 2016 in Quebec.

| 18 months | |
|---|---|
| Before May 2013 | MMR (MMR II®/Merck) + DTaP-IPV-Hib (Pediacel®/Sanofi) |
| May 2013–September 2014 | MMRV (Priorix-Tetra®/GSK) + DTaP-IPV-Hib (Infanrix-IPV-Hib®/GSK) |
| October 2014–December 2014 | MMRV (Priorix-Tetra®/GSK) + DTaP-HB-IPV-Hib (Infanrix-hexa®/GSK) |
| Since January 2015 | MMRV (Proquad®/Merck) + DTaP-HB-IPV-Hib (Infanrix-hexa®/GSK) |

## 2. Methods

In Quebec, health professionals are legally required to report any unusual adverse event following immunization (AEFI) if they suspect a vaccine link. In this investigation, LLR included local injection site reactions (redness, swelling, pain) reported by a health professional as meeting at least one of the following criteria: (1) Extending beyond the nearest joint; or (2) Lasting $\geq$ 4 days; or (3) Abscess (sterile or infectious); or (4) Cellulitis treated with antibiotics.

Investigation was first undertaken based upon the series of cases (hypotheses 1–5). Then a case-control study was conducted with a ratio of 5 controls per case to explore hypotheses 6 to 9. Cases were patients born between January 2012 and April 2015 with a LLR reported to QVAERS following MMR ± V or DTaP-IPV-Hib ± HB administered between 16 and 23 months of age. Controls were randomly selected from the provincial universal medicare database among children born during the same period.

Vaccination data for cases and controls were extracted from the provincial immunization registry. For those with incomplete data (26 cases and 258 controls), a phone survey was conducted between January 11 and February 4, 2017 to collect information regarding their "18-month" vaccines. Parents were asked to read the MMR ± V and DTaP-IPV-Hib ± HB history written in their child's vaccination booklet. When information remained incomplete, the child's 18-month vaccine provider was contacted. Cases and controls who had received no MMRV or DTaP-IPV-Hib ± HB dose between 16 and 23 months of age were excluded. Administration route reported by health professionals in different vaccination sources was considered as accurate when available. In Quebec, the preferred site for the administration of the 18-month vaccines is the upper arms. However, the thigh may be used when deemed appropriate.

While MMR ± V is administered subcutaneously and DTaP-IPV-Hib ± HB intramuscularly, when they were given in the same limb (slightly apart from each other), it was not possible to attribute the LLR to a specific vaccine. Attribution of the LLR to a specific vaccine required the vaccine alone to have been administered in the affected limb. The risk of LLR relative to the appropriate comparator groups (depending upon the causal hypothesis being tested, as individually specified below) was estimated using the odds ratio with 95% confidence interval (95% CI). Proportions were compared with two-tailed Chi Square test or exact Fisher test with statistical significance defined as $p < 0.05$. All analyses were performed with SAS 9.4 (SAS Institute Inc. Cary, NC).

This investigation was conducted under the legal authority conferred by the Quebec Public Health Act and did not require

**Table 2**
Hypotheses evaluated in this investigation to identify the cause of increased LLR reporting.

| Number | Hypothesis |
|---|---|
| Hypothesis 1 | LLRs are associated with a specific vaccine lot |
| Hypothesis 2 | LLRs are associated with errors in the route of administration |
| Hypothesis 3 | LLRs are associated with MMRV being the first MMR-containing vaccine |
| Hypothesis 4 | LLRs are associated with a reporting bias due to a new product |
| Hypothesis 5 | LLRs are associated with a specific vaccine (ProQuad® or Infanrix-hexa®) |
| Hypothesis 6 | The risk of LLR related to MMRV is greater with ProQuad® than Priorix-Tetra® |
| Hypothesis 7 | The risk of LLR related to DTaP-IPV-Hib is greater with Infanrix-hexa® than with Infanrix-IPV-Hib® |
| Hypothesis 8 | The risk of LLR is associated with the co-administration of Infanrix-hexa® and ProQuad® in the same limb |
| Hypothesis 9 | The risk of LLR is greater with the administration of Infanrix-hexa® and ProQuad® during a single compared to separate visits |

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submission to a Research Ethics Board or consent to access the information recorded in the QVAERS database and immunization registry. Verbal consent was obtained from the guardians of all participants contacted during the phone survey.

## 3. Results

### 3.1. Characteristics of cases and controls

Between January 2014 and September 2016, 112 cases of LLR following immunization with MMR ± V or DTaP-VPI-Hib ± HB were reported to the QVAERS database. Of these, 16 (14%) were excluded because they received only MMR vaccine (n = 10), had been immunized after 23 months of age (n = 4) or had incomplete information (n = 2) (Fig. 1). Among the 96 LLR cases that occurred between March 2014 and September 2016 who were included in the analysis, all had received MMRV (89 ProQuad®), and 95 had received DTaP-IPV-Hib ± HB (90 Infanrix-hexa®). In only 6% (n = 6) of cases, Infanrix-hexa® rather than Infanrix-IPV-Hib® was administered at 6 months of age. Increased reporting of LLR was clearly evident in early 2015, but appears to have started since October 2014 (Fig. 2). Among the 96 cases, 44 (46%) had a cellulitis and 52 (54%) had an injection site reaction extending beyond the nearest joint (n = 12 (23%)), lasting ≥ 4 days (n = 18 (35%)) or with both signs (n = 5 (10%)). There was no case of nodule or sterile/infectious abscess. We had information on LLR duration for 89 of the 96 cases (93%). For 90% of cases, LLR started between 4 and 48 h after vaccination and lasted less than 7 days. Overall, 72 (75%) sought medical care and 7 (7%) were hospitalized, including 6 with cellulitis. All but one case received MMRV and DTaP-IPV-Hib ± HB at the same visit: 55 (58%) in the same limb, 39 (41%) in different limbs and for one the information was unknown (Fig. 1). Most (86%) cases received their 18-month vaccines in their upper arms as recommended.

Among the 800 randomly selected controls, 306 were excluded: 234 for which the vaccines received or the age at immunization did not fulfill the inclusion criteria; 66 with no vaccination record; and 6 who were not vaccinated. This left 494 controls for the analysis. A phone number was available for a greater proportion of cases compared to controls (100% versus 87%, p-value = 0.02), but the proportion of parents who agreed to participate was similar for cases and controls (92% versus 89%, p-value = 0.6). Cases and controls were similar with respect to sex, age at vaccination and type of vaccine provider (Supplementary file 1). The vaccines used were similar and reflected the changes in the vaccination schedule, the antigen combinations and vaccine brands (Fig. 3).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.09.049.

### 3.2. Hypotheses tested to identify the cause of increased LLR reporting

#### Hypothesis 1. LLRs are associated with a specific vaccine lot

LLRs were associated with 21 lots for ProQuad® (lot number available for 81/89 cases) and 17 lots of Infanrix-hexa® (lot number available for 71/90 cases). Accordingly, this hypothesis appeared very unlikely.

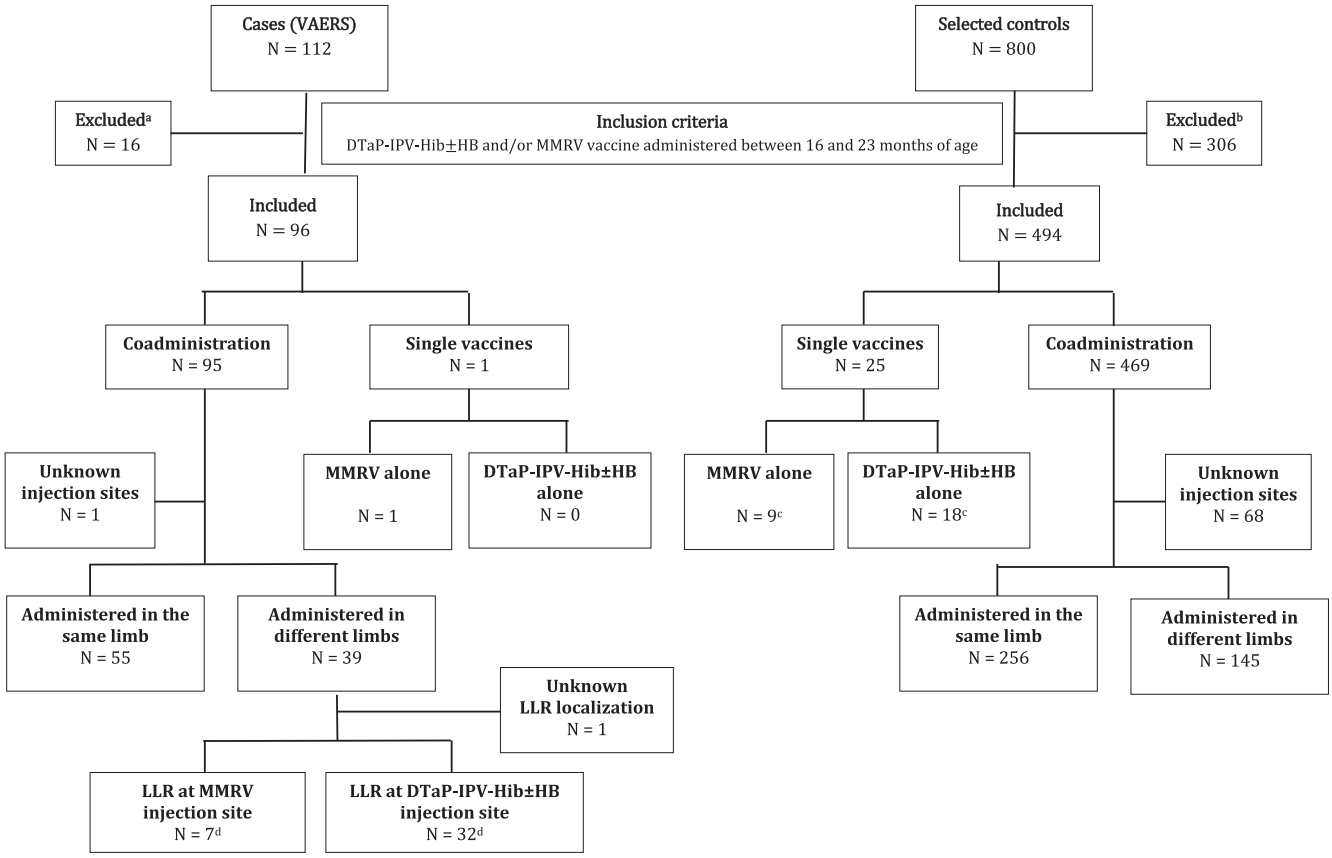


**Fig. 1.** Flow chart of large local reaction (LLR) cases and controls. [a]See text for case exclusion criteria. [b]See text for control exclusion criteria. 234 controls were excluded because the vaccines received or the age at immunization not fulfill the inclusion criteria (99 without DTaP-IPV-Hib ± HB or MMR ± V between 16 and 23 months, 89 with MMR or DTaP-IPV, 21 with 2 doses of DTaP-IPV-Hib ± HB or MMR ± V between 16 and 23 months, 9 who received vaccines recommended at 12 months, 8 who received vaccines after the extraction date for cases, 5 with unknown vaccine name and 3 vaccinated outside Quebec. [c]Including two who received MMRV and DTaP-IPV-Hib ± HB vaccines at different visits. [d]Including one who had an ISR on both limbs.

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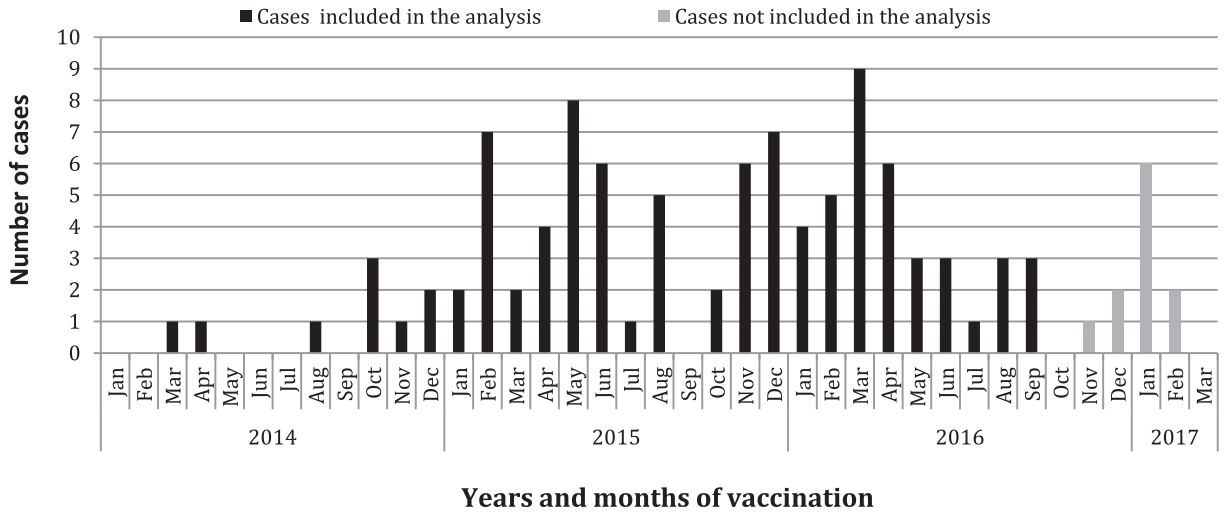


**Fig. 2.** Number of LLR cases following MMR ± V or DTaP-IPV-Hib ± HB vaccines reported to the passive surveillance system by year and month of vaccination on 15th March 2017.

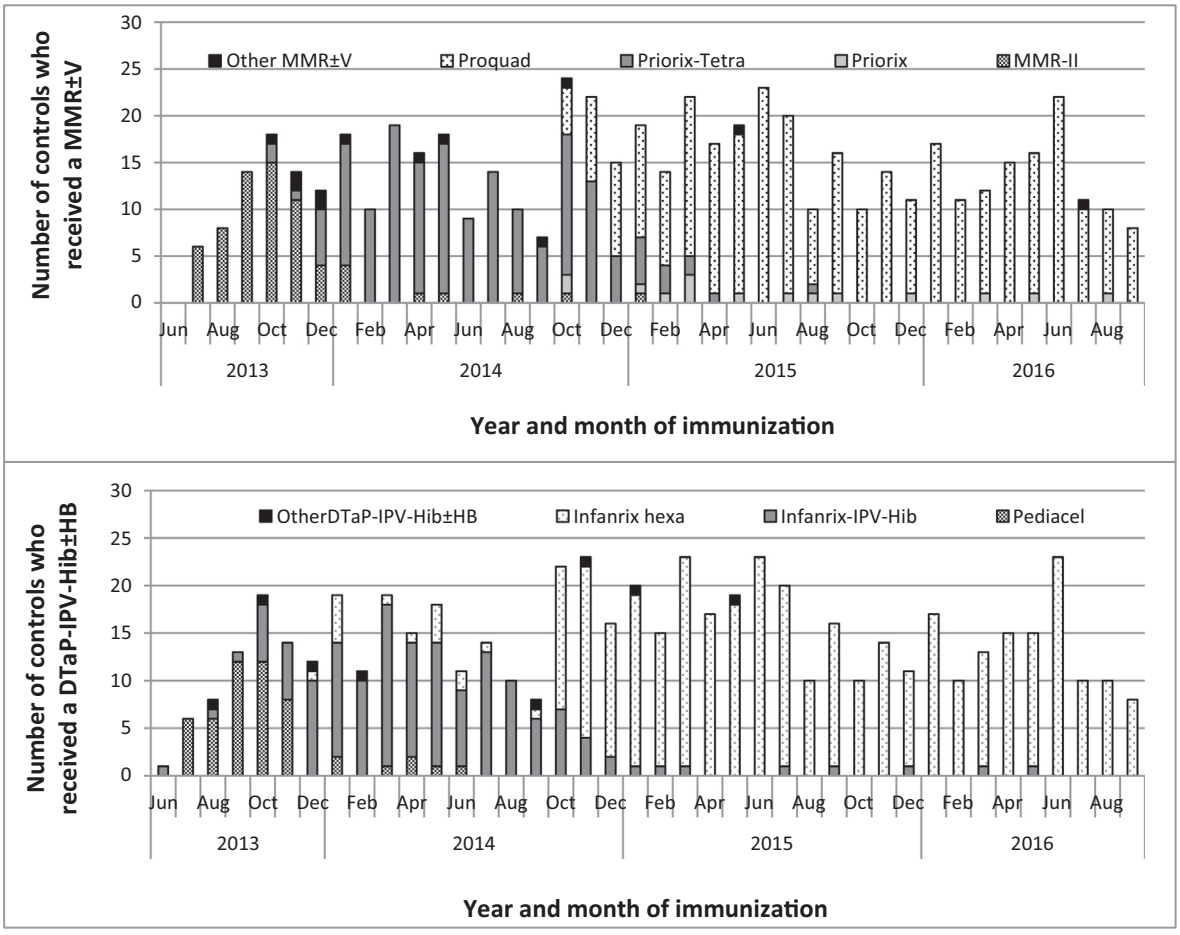


**Fig. 3.** Type of MMR ± V and DTaP-IPV-Hib ± HB vaccines received by controls immunized between June 2013 and September 2016.

### Hypothesis 2. LLRs are associated with errors in the route of administration

Among the 78/89 cases with information for ProQuad®, 93% (72/78) had it appropriately administered sub-cutaneously and among the 87/90 cases with information on Infanrix-hexa® all received it intramuscularly as recommended. Although this was not a direct assessment of the route of administration and may be subject to errors, this hypothesis appeared very unlikely.

### Hypothesis 3. LLRs are associated with MMRV being the first MMR-containing vaccine

Among the 89 cases who received ProQuad at 18 months, 82 had previously received MMR at 12 months of age. Given the few

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cases who received MMRV as first MMR-containing vaccine, this hypothesis appeared very unlikely.

### Hypothesis 4. LLRs are associated with a reporting bias due to a new product

We are not aware of any concerns from providers or parents or change in the AEFI reporting related to use of a new product during the study period. The number of reported cases had increased since October 2014 and remained steadily high not only at the beginning of 2015 but also in 2016 and 2017 (Fig. 2). While over-reporting with administration of a new product cannot be ruled out, this hypothesis seems unlikely given it was sustained over a prolonged period and that 18-month vaccine coverage rates were similar over the years [1,2].

### Hypothesis 5. LLRs are associated with a specific vaccine (ProQuad® or Infanrix-hexa®)

Among the 39 cases who were immunized in different limbs, 77% (n = 30) of the LLRs were located at the Infanrix-hexa® site, 5% (n = 2) at Infanrix-IPV-Hib® site, 18% (n = 7) at the ProQuad® site and none at the Priorix-Tetra® site (Table 3). One patient had LLR in both limbs with Infanrix-hexa® and Proquad® and for another, the vaccine injected at the LLR site could not be determined. Infanrix-hexa® was the product most associated with LLRs but Proquad® was also involved.

### Hypothesis 6. The risk of LLR related to MMRV is greater with ProQuad® than Priorix-Tetra®.

Among the 40 cases who were immunized in different limbs (n = 39) or who received MMRV alone (n = 1), 8 cases had their LLR at an MMRV site and all had received ProQuad® (7 coadministered and 1 alone). Among the 154 controls who had received MMRV and DTaP-IPV-Hib ± HB on different limbs (n = 145) or MMRV alone (n = 9), 64% (n = 99) had received ProQuad® (p-value = 0.052, odds ratio cannot be calculated) (Table 3). The risk of LLR attributable to ProQuad® was not significantly different when co-administered with Infanrix-hexa® in a different limb at the same visit (7/8 cases and 93/98 controls) than when administered alone (1/8 cases and 5/98 controls) (OR 0.38, 95%CI: 0.04–3.68). LLRs were more frequent with ProQuad® than Priorix-Tetra® but this did not reach statistical significance.

### Hypothesis 7. The risk of LLR related to DTaP-IPV-Hib ± HB is greater with Infanrix-hexa® than with Infanrix-IPV-Hib®

Among the 39 cases who received their DTaP-IPV-Hib ± HB in a different limb than MMRV, 32 had their LLR at the DTaP-IPV-Hib ± HB site. Infanrix-hexa® was the product given to 94% (n = 30) of these cases compared to 72% (117/163) among controls (OR = 5.9, 95%CI: 1.4–25.7) (Table 3). The risk of LLR attributable to Infanrix-hexa® was the same when co-administered with ProQuad® in different limbs (87%, 26/30 cases and 87%, 93/107 controls) or with Priorix-Tetra®(4/30 cases and 14/107) (p-value = 1.0). LLRs were significantly more frequent with Infanrix-hexa® than with Infanrix-IPV-Hib® vaccine.

### Hypothesis 8. The risk of LLR is associated with the co-administration of Infanrix-hexa® and ProQuad® in the same limb.

Among participants who received their two vaccines at the same visit, the odds of LLR when they were administered in the

**Table 3**
Vaccines received between 16 and 23 months of age for the 96 cases and 494 controls included in the analysis.

| | Infanrix-hexa® | | DTaP-IPV-Hib | | No DTaP-IPV-Hib ± HB | |
|---|---|---|---|---|---|---|
| | Cases **N = 90** | Controls **N = 358** | Cases **N = 5** | Controls **N = 129** | Cases **N = 1** | Controls **N = 7** |
| **DTaP-IPV-Hib ± HB alone (No MMRV)** | **0 (0%)** | **8 (2%)** | **0 (0%)** | **8 (6%)** | | |
| **Any MMRV** | | | | | | |
| No DTaP-IPV-Hib ± HB | | | | | 1 (100%) | 7 (100%) |
| DTaP-IPV-Hib ± HB at separate visit | | 2 (0.6%) | | | | |
| **Co-administered with DTaP-IPV-Hib ± HB** | **90 (100%)** | **348 (97%)** | **5 (100%)** | **121 (94%)** | | |
| Unknown injection site[a] | 1 (1%) | 42 (12%) | 0 (0%) | 26 (22%) | | |
| In the same limb[a] | 52 (58%) | 199 (57%) | 3 (60%) | 57 (47%) | | |
| In different limbs[a] | **37 (41%)** | **107 (31%)** | **2 (40%)** | **38 (31%)** | | |
| *LLR at MMRV site*[b] | *7*[c] *(19%)* | *na* | *0 (0%)* | *na* | *1* | *na* |
| *LLR at DTaP-IPV-Hib ± HB site*[b] | *30*[c] *(81%)* | *na* | *2 (100%)* | *na* | | |
| *LLR location unknown*[b] | *1 (0%)* | *na* | *0 (0%)* | *na* | | |
| **ProQuad®** | | | | | | |
| No DTaP-IPV-Hib ± HB | | | | | 1 (100%) | 4 (57%) |
| DTaP-IPV-Hib ± HB at separate visit | | 1 (0.3%) | | | | |
| **Co-administered with DTaP-IPV-Hib ± HB** | **85 (94%)** | **304 (85%)** | **3 (60%)** | **5 (4%)** | | |
| Unknown injection site[a] | 1 (1%) | 29 (9%) | 0 (0%) | 1 (20%) | | |
| In the same limb[a] | 51 (60%) | 182 (60%) | 2 (67%) | 3 (60%) | | |
| In different limbs[a] | **33 (39%)** | **93 (31%)** | **1 (33%)** | **1 (20%)** | | |
| *LLR at ProQuad® site*[b] | *7*[c] *(21%)* | *na* | *0 (0%)* | *na* | *1* | *na* |
| *LLR at DTaP-IPV-Hib ± HB site*[b] | *26*[c] *(79%)* | *na* | *1 (100%)* | *na* | | |
| *LLR location unknown*[b] | *1 (0%)* | *na* | *0 (0%)* | *na* | | |
| **Priorix-Tetra®** | | | | | | |
| No DTaP-IPV-Hib ± HB | | | | | 0 | 3 (43%) |
| DTaP-IPV-Hib ± HB at separate visit | | 1 (0.3%) | | | | |
| **Co-administered with DTaP-IPV-Hib ± HB** | **5 (6%)** | **44 (12%)** | **2 (40%)** | **116 (90%)** | | |
| Unknown injection site[a] | 0 (0%) | 13 (29%) | 0 (0%) | 25 (21%) | | |
| In the same limb[a] | 1 (20%) | 17 (39%) | 1 (50%) | 54 (47%) | | |
| In different limbs[a] | **4 (80%)** | **14 (32%)** | **1 (50%)** | **37 (32%)** | | |
| *LLR at Priorix-Tetra® site*[b] | *0 (0%)* | *na* | *0 (0%)* | *na* | | |
| *LLR at DTaP-IPV-Hib ± HB site*[b] | *4 (100%)* | *na* | *1 (100%)* | *na* | | |
| *LLR location unknown*[b] | *0 (0%)* | *na* | *0 (0%)* | *na* | | |

[a] Proportions among those with co-administred vaccines.
[b] Proportions among those who received vaccines in different limbs.
[c] One case had LLR at both limbs/Na: Not applicable.

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same limb (51/182) was not significantly greater than when administered in separate limbs (33/93) (OR 0.79, 95%CI: 0.48–1.31) (Table 3). The administration of the two vaccines in the same limb did not increase the risk of LLR.

**Hypothesis 9. The risk of LLR is greater with the administration of Infanrix-hexa® and ProQuad® during a single compared to separate visits.**

All 26/26 cases with LLR attributable to lnfanrix-hexa® had received it at the same visit as ProQuad® whereas 10/103 (10%) of controls had received it during a separate visit (p = 0.2) (Table 3). One (13%) of the 8 LLRs attributable to ProQuad® occurred in children who received it alone compared to 5/98 (5%) for controls (p = 0.21). The administration of the two vaccines during a single visit did not increase the risk of LLR.

## 4. Discussion

An excess of LLR following the 18-month vaccine visit in Quebec followed two changes in vaccine products given at this visit. When several vaccines are co-administered, it may be difficult to determine which caused a systemic AEFI but this should be easier for LLR. In this investigation, it was nevertheless challenging to identify the cause as over half of LLR cases had received their two vaccines in the same limb. Ultimately, cases who had DTaP-IPV-Hib ± HB and MMRV administered in different limbs were the most informative. In these latter patients, most LLRs were associated with Infanrix-hexa® (77%) although ProQuad® was also implicated (18%). The OR of LLR was 6-fold higher with Infanrix-hexa® than with Infanrix-IPV-Hib®. The risk of LLR seemed higher after co-administration with ProQuad® compared to Priorix-Tetra®, but the analysis was limited by the small number of cases who received Priorix-Tetra®. The risk of LLR was not greater when Infanrix-hexa® and ProQuad® were administered in the same limb or in separate limbs at a single visit. On balance this investigation suggests that most LLRs were causally associated with the hexavalent vaccine Infanrix-hexa®.

To our knowledge, the Quebec vaccination schedule is not used elsewhere. In published clinical trials, the frequency of injection site reactions was similar with Infanrix-hexa® or Infanrix-IPV-Hib® given as separate injections with HB vaccine. Following immunization at 12 to 23 months of age with Infanrix-hexa® alone or co-administered with a first dose of Priorix-Tetra®, swelling (≥20 mm) was reported by 9.3% and 4.7% vaccinees, and grade 3 local pain (spontaneously painful or crying when the vaccinated limb was moved) by 2% and 4%, respectively [3]. At 3, 5 and 11 months of age, swelling (≥20 mm) and grade 3 local pain at the DTaP-IPV-Hib ± HB injection site was reported by 6.2% and 0.4% of children who received Infanrix-hexa® and 1.7% and 0.2% of children who received Infanrix-IPV-Hib® + HB [4]. Swelling (≥20 mm) at the DTaP-HB-IPV injection site after any dose was reported by 4.1% and 3.9% of children who received DTaP-HB-IPV or DTaP-HB-IPV + Hib at 3, 5 and 11 months, and grade 3 local pain by 1.6% and 1.6%, respectively. These frequencies were similar after each dose [5]. In contrast, during our investigation only 4 LLRs were reported in 2015 after the 2-month and 4 after the 4-month vaccines, corresponding to 4.7/100 000 vaccinees, compared with 62.5/100 000 vaccinees reported after the 18-month vaccines.

In a multi-center open-label randomized clinical trial conducted among 952 children aged 12–23 months in Germany, local reactions at the ProQuad® site were more frequent after immunization with ProQuad® and Infanrix-hexa® administered in different limbs than after immunization with ProQuad® alone (31.6% vs 19.7% for any reaction and 9.7% vs 2.6% for swelling) [6]. This increase had also been observed after immunization with ProQuad® and DTaP + HB vaccines [7]. In the Germany study, local reactions were reported more frequently at Infanrix-hexa® than ProQuad® injection sites but co-administering ProQuad® did not increase the frequency of local reaction at the Infanrix-hexa® injection site (65.4% vs 65.3% for any reactions and 38% vs 38.9 for swelling) [6]. These studies did not suggest that immunizing 18-month old children with Infanrix-hexa® alone or with ProQuad® would cause a significant increase in LLR. However, they were underpowered to detect an increase in the risk of rare but more serious LLR.

One difficulty faced by this investigation was related to the information reported to QVAERS. On the reporting form, practitioners were supposed to identify only the vaccine "causing" the LLR. When two vaccines were given in the same limb, both were reported. The increased risk of LLR associated with Infanrix-hexa® therefore led to a significant increase related to ProQuad® as well. This reporting practice did not prevent the passive surveillance system from detecting the LLR increase but the surveillance signal initially appeared associated with ProQuad®. Reporting only the vaccine causing the LLR facilitates surveillance activities but prevented us from determining if co-administration with another vaccine in a different limb increased the LLR risk. It required thorough search of the case immunization history to identify co-administered vaccines that had not been reported. Even when MMRV and DTaP-IPV-Hib ± HB were administered in different limbs substantial efforts were required to link vaccine and limb and attribute the LLR to the proper product since providers and reporters were not necessarily the same or had access to the information. After this investigation, it was recommended in Quebec that LLR reports should include a list of all vaccines administered with a clear indication of the vaccine specifically linked to and causing the LLR.

Among reported LLRs, 46% were diagnosed as cellulitis and treated with antibiotics although none were confirmed by culture and were unlikely to be injection related bacterial cellulitis. Extensive limb swelling caused by a local inflammatory reaction to the DTaP booster dose is a well-known phenomenon, although more frequently described after the DTaP preschool than toddler dose [8–11]. Extensive limb swelling can mimic cellulitis symptoms making it difficult to rule out bacterial infection [12,13]. It is not uncommon for these cases to receive antibiotics as a precaution although post-immunization bacterial infections are rare in modern vaccination settings [12]. Contaminated vials would have instead caused injection site abscesses as reported in the past [14,15]. No abscess was reported in this investigation, suggesting that bacterial infections were unlikely and patients may have received antibiotics unnecessarily. A clinical diagnosis of bacterial cellulitis versus sterile inflammatory reaction to vaccine may be informed by timing in relation to immunization, symptom progression and response to antibiotics if prescribed [16,17].

This study has limitations including those typically associated with passive surveillance such as under-reporting, data quality and incomplete data entry [16,18]. The estimation of 1 LLR per 2000 vaccinees under-estimated the true frequency but the proportion of under-reporting could not be quantified. In our study, controls were included independently of their LLR status. Except for a few controls who were called, we did not gather the information regarding LLR. Among the controls called, only 2 had minimal injection site reactions but did not meet the criteria for LLR. LLR following vaccination was not a common event in children. This scenario of minor non differential misclassification will only slightly underestimate the OR and was deemed acceptable for the purpose of this investigation [19]. Despite a high survey participation rate, the injection site remained unknown for 15% of controls and 1% of cases. The use of multiple data sources to document vaccination history sometimes resulted in conflicting

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information that possibly led to misclassification of vaccines or injection sites. Using a population-based registry to select controls allowed us to obtain a representative sample, but vaccination information could not be documented for 8%. These children may have differed from those included in the study with respect to vaccination protocols, but their small number (n = 66) means this would have had minimal impact on findings.

In Quebec, HB immunization has included three groups: those at high risk; neonates born to chronic HB carrier mothers; and grade 4 children. The universal school-based program targeting grade 4 children started in 1994 and has coverage of ~85%, leading to near elimination of acute HB in Quebeckers <30 years old [20]. Despite this excellent performance, Quebec moved to an infant program replacing Infanrix-IPV-Hib® with Infanrix-hexa® in the infant schedule. This change may have increased HB vaccine coverage by ~10%, given infant pentavalent vaccine coverage was ~95%. Notwithstanding the increase in LLRs vaccine coverage at 18 months remained similar in 2014 and 2016 (as assessed at 2 years of age) [1,2]. Given the improved HB vaccine coverage, benefit-risk analysis likely still favours ongoing use of Infanrix-hexa® with informed parental consent.

## 5. Conclusion

The increase in reported LLR at 18 months of age reported through post-marketing passive surveillance in Quebec was likely due to the introduction of Infanrix-hexa®. The co-administration of Infanrix-hexa® and ProQuad® in the same limb did not further increase that risk.

## 6. Contributors

MK, MNB, ET, JGZ, ML and GDS contributed meaningfully to the conception and design of this investigation. MK, MNB, JGZ and GDS collected the data, performed analyses, interpreted the results and drafted the manuscript. All authors contributed meaningfully to the interpretation of data and revised the manuscript critically for important intellectual content as well as final approval of the final version of the manuscript.

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## Conflicts of interest

GDS has received grants for investigator-initiated studies from GSK and Pfizer and provided paid expert testimony for the Ontario Nurses Association, the Quebec Ministry of Justice and GSK. Other authors have no conflicts of interest to declare.

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