資料８

Self-controlled case series (SCCS) methodの概要

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Self-controlled case series (SCCS) method

HJ Whitaker et al. Tutorial in Biostatistics:The self-controlled case series method；Statist. Med. 2005;　0：1-31

- 背景：90年代、MMRと無菌性髄膜炎との関連を検証するために用いられた。
  - 早急に検証することが要請されていたが、control群を必要とするstudyは時間がかかった。
  - 以前から用いられていた”cross-over method”を応用した。
- 現在ではワクチン以外の、複数回の暴露機会（例：カテーテル検査と心筋梗塞など）とoutcomeの関連を検証する目的で応用されている。

利点と制限

- 利点
  1. Caseのみで実施可能
  2. 性、経済社会的背景、遺伝学的背景、個体の弱さ（frailty）、基礎疾患などの交絡因子に左右されない
  3. 年齢やoutcome（event）の発生頻度をmodel（数式）に挿入可能
  4. 条件によってはRetrospective cohort methodよりもはるかに効率がよい

- 制限
  1. Outcomeの発生に暴露の条件が左右されないことが必要
  2. Eventが反復するものでない場合、そのeventが発生する確率は小さいことが必要
  3. 算出可能なのはrelative incidenceのみで、absolute incidenceは算出できない
  4. Eventが発生する時間や年齢にばらつきがなければならない

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Sudden Unexpected Deaths and Vaccinations during the First Two Years of Life in Italy: A Case Series Study

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Introduction

Signal:

- 2003 in Germany: SUD↑- ass'n with Hexavac?
- Nov 2000- Jun 2003 : 3 death (2 y/o) within 48 hrs following the administration of 4th dose.
- SMR = 23

Italy: 2nd largest market of Hexavac. No signal events

Methods

- Study population: All children who died of SUD b/w 31-729 days of age in 1999-2004
- Case-series methodology
  - case only
  - risk period: 0-14 days following vaccination
  - control period: the remaining observation period
  - Exposed: event+ during the risk period
  - Not-exposed: event+ during the control period
  - Obtain Rate ratio (RR)

→同じpop'nを対象としたCohort study で得られるRR に近似できる（と、されている）。Bias が減る。

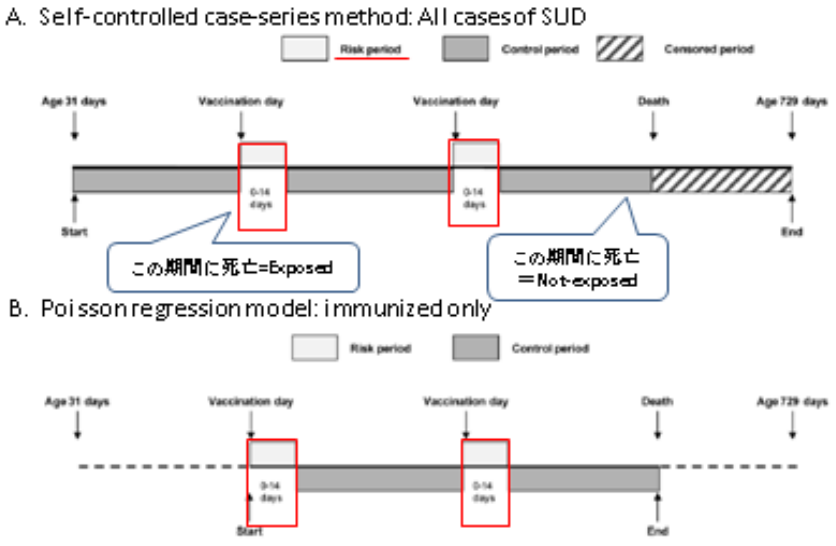

Figure 1. Description of the observation period for a hypothetical subject included in the study. Legend A. Self-controlled case-series method for censoring, perturbed or curtailed post-event exposures [19] Legend B. Poisson regression model.
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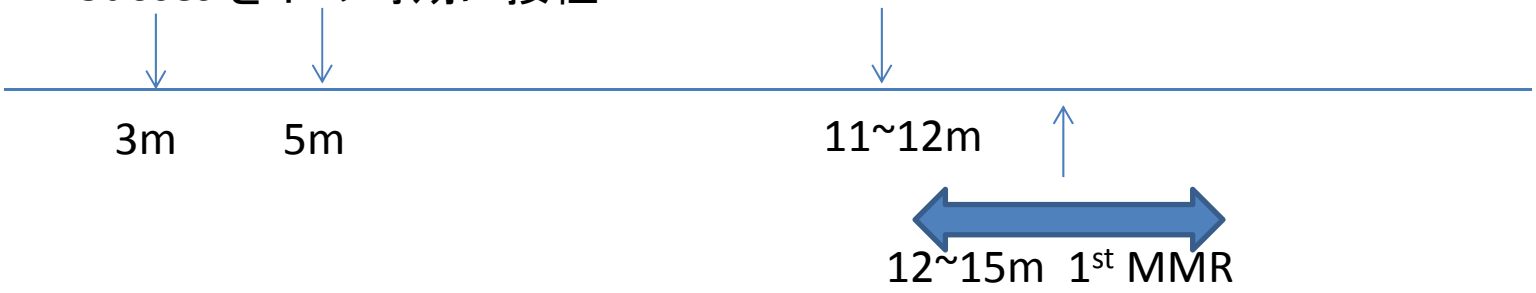
Methods-cont'd

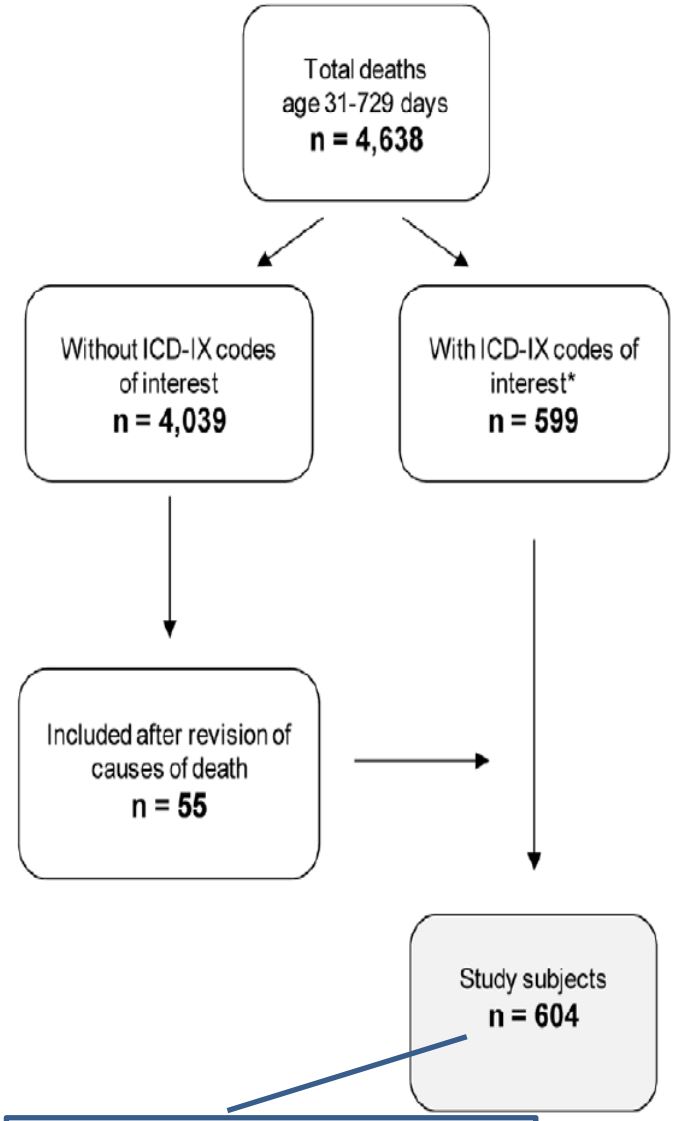
- Case finding : death certification and ICD code
  - All individual records of death were reviewed
- Vaccination histories: Local health units(LHU)

- diphteria, tetanus,pertussis, poliomyelitis, hepatitis B, Hib は 3doses を下の時期に接種



- 95% の小児が2歳になるまでに完了
- 95%がLUHで接種。 その他の医療機関で接種した場合も、医師にはLUHへの報告が求められている。
- 1歳未満の児が受けたワクチンのうち、96%がHexavac

Result



このうち244（40%）が少なくとも1回ワクチン接種あり

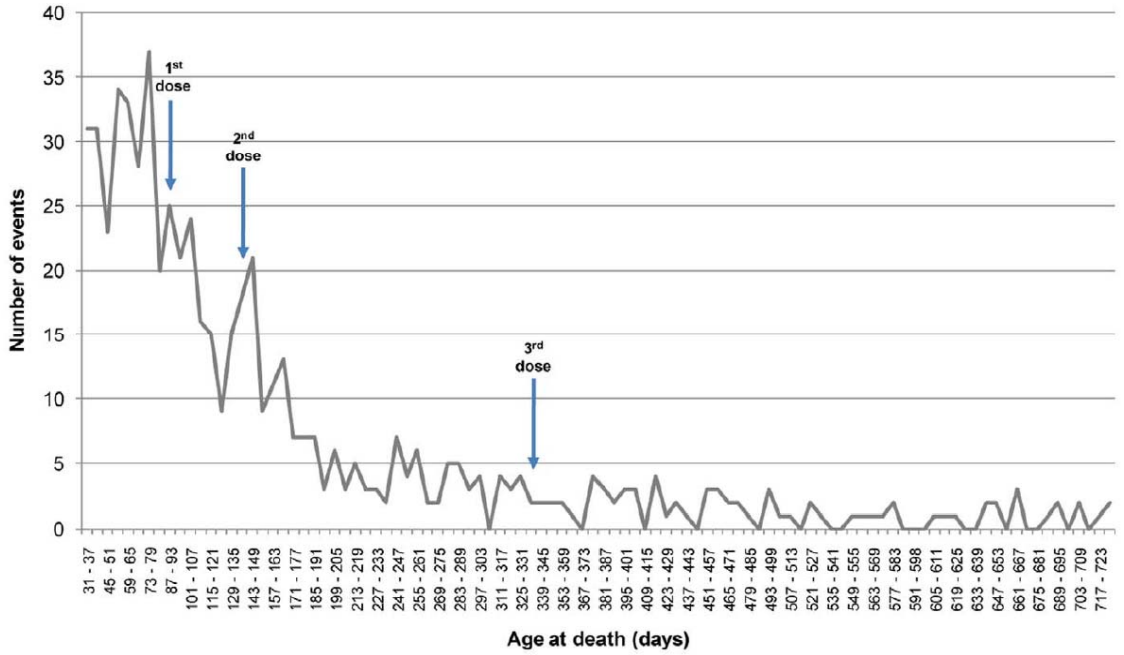


Figure 3. Distribution of the 604 events of SUD included in the study by age of death. Legend. The three arrows indicate the median age at first, second and third vaccine dose.
doi:10.1371/journal.pone.0016363.g003

Figure 2. Selection of the study population, age 31–729 days, Italy 1999–2004. Legend. *One subject was excluded because the date of birth was unknown.
doi:10.1371/journal.pone.0016363.g002

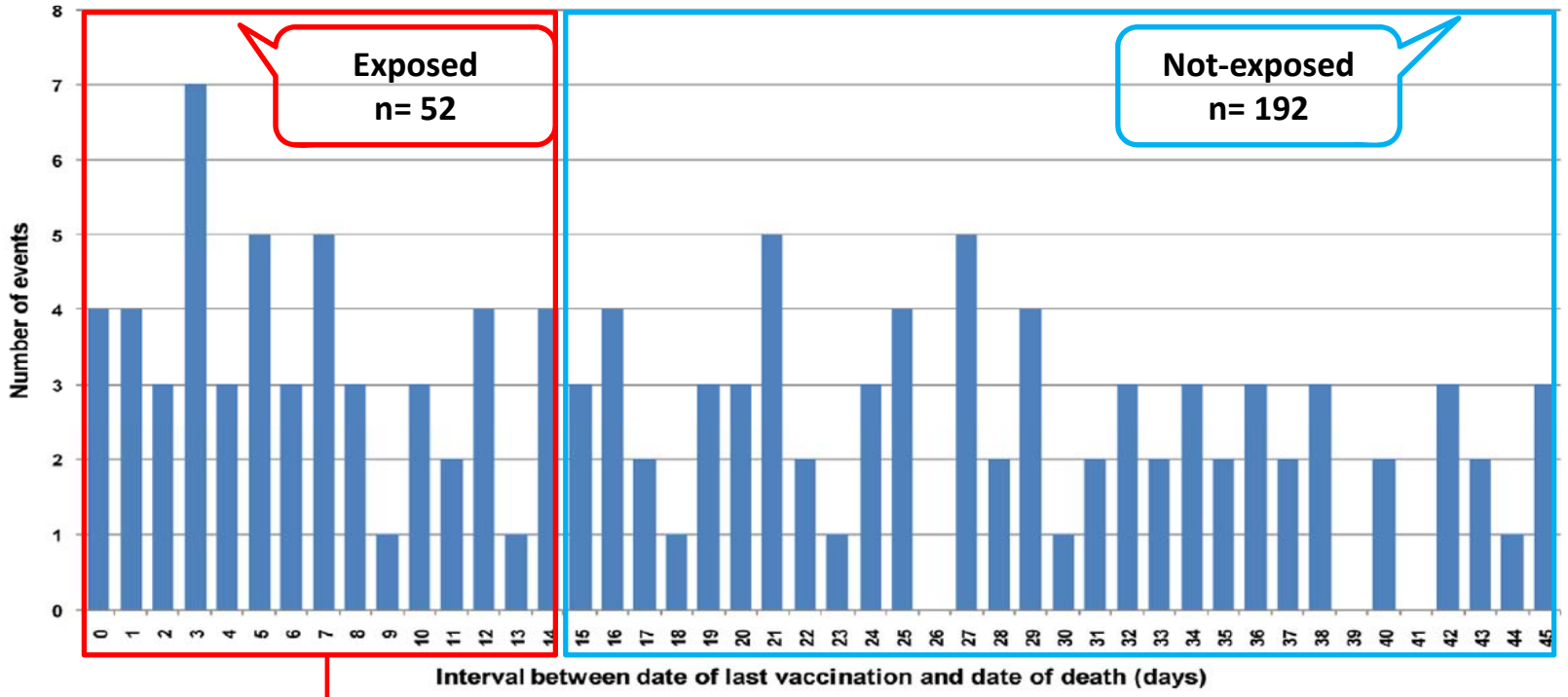


Figure 4. Distribution of immunised subjects by interval between date of vaccination and date of death. * Legend. *Only events occurring within 45 days from vaccination are shown.
doi:10.1371/journal.pone.0016363.g004

Table 3. Rate ratio of sudden unexpected deaths in infants of age 31–729 days by risk period (following any vaccination) and dose, Italy 1999–2004.

	Risk period: 0–1 days		Risk period: 0–7 days		Risk period: 0–14 days	
	N	RR adj[1] (95% CI)	N	RR adj[1] (95% CI)	N	RR adj[1] (95% CI)
All doses	8	1.2 (0.4–2.1)	34	1.3 (0.9–1.9)	52	1.1 (0.8–1.5)
1st dose	5	1.2 (0.4–2.5)	24	1.5 (1.0–2.3)	34	1.2 (0.8–1.6)
2nd – 3rd dose	3	1.2 (0.3–3.0)	10	1.0 (0.4–1.9)	18	1.0 (0.6–1.6)

N: Number of deaths; RR adj: adjusted Rate Ratio; CI: Confidence Interval.
[1]RRs are estimated according to the self controlled case-series method for censoring, perturbed or curtailed post-event exposures [19] and adjusted by age group (31–80; 81–100; 101–120; 121–180; 181–360; 361–729).
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Table 4. Rate ratio of sudden unexpected deaths in infants of age 31–729 days by risk period and type of vaccine, Italy 1999–2004.

Vaccine groups	Risk period: 0–1 days			Risk period: 0–7 days			Risk period: 0–14 days		
	N	P-d	RR adj[1] (95% CI)	N	P-d	RR adj[1] (95% CI)	N	P-d	RR adj[1] (95% CI)
Any vaccine	**8**	**864**	**1.1 (0.5–2.4)**	**34**	**3355**	**1.4 (0.9–2.1)**	**52**	**6104**	**1.1 (0.8–1.6)**
All concomitant administration of six antigens	**7**	**593**	**1.5 (0.7–3.5)**	**30**	**2276**	**1.8 (1.1–2.8)**	**44**	**4112**	**1.5 (1.0–2.2)**
Hexavalent products[2]	4	322	1.5 (0.6–4.2)	18	1231	2.0 (1.2–3.5)	25	2228	1.5 (0.9–2.4)
Hexavac	1	160	0.7 (0.1–5.5)	12	599	2.8 (1.4–5.3)	13	1075	1.6 (0.8–3.1)
Infanrix hexa	3	160	2.3 (0.8–7.7)	6	624	1.4 (0.6–3.1)	12	1138	1.5 (0.8–2.7)
Other concomitant administration of six antigens	3	271	1.4 (0.4–4.8)	12	1045	1.6 (0.8–3.0)	19	1884	1.4 (0.8–2.3)
Others	**1**	**271**	**0.5 (0.1–3.4)**	**4**	**1079**	**0.5 (0.2–1.4)**	**8**	**1978**	**0.6 (0.3–1.1)**
Control period	**192**	**29875**	**1**	**192**	**29875**	**1**	**192**	**29875**	**1**

N: Number of deaths; P-d: Person-days at risk; RR adj: adjusted Rate Ratio; CI: Confidence Interval.
[1]RRs are estimated by the Poisson regression model and adjusted by age group (31–80; 81–100; 101–120; 121–180; 181–360; 361–729).
[2]The information of the brand name of the hexavalent product was missing for 1 infant (the event occurred in the control period).
doi:10.1371/journal.pone.0016363.t004

Table 5. Rate ratio of sudden unexpected deaths in infants of age 31–729 days for the risk period 0–14 days following vaccination with a combination of six antigens by dose, Italy 1999–2004.

	First dose			Second and third dose		
	N	P-d	RR adj[1] (95% CI)	N	P-d	RR adj[1] (95% CI)
Any administration of six antigens	**30**	**2457**	**1.9 (1.0–3.4)**	**14**	**1655**	**1.2 (0.7–2.1)**
Hexavalent products[2]	**18**	**1263**	**2.2 (1.1–4.4)**	**7**	**965**	**1.0 (0.5–2.1)**
Hexavac	10	580	2.7 (1.1–6.9)	3	480	0.8 (0.3–2.6)
Infanrix hexa	8	668	1.9 (0.8–4.2)	4	485	1.1 (0.5–2.9)
Other concomitant administration of six antigens	**12**	**1194**	**1.6 (0.8–3.2)**	**7**	**690**	**1.4 (0.6–3.0)**
Control period	**192**	**29875**	**1**	**192**	**29875**	**1**

N: Number of deaths; P-d: Person-days at risk; RR adj: adjusted Rate Ratio; CI: Confidence Interval.
[1]RRs are estimated by the Poisson regression model and adjusted by age group (31–80; 81–100; 101–120; 121–180; 181–360; 361–729 for the first dose; 31–180; 181–360; 361–729 for the second-third dose).
[2]The information on the brand name of the hexavalent product was missing for 1 infant (the event occurred in the control period).
doi:10.1371/journal.pone.0016363.t005

Conclusion and discussion

- Hexavac 接種後7日以内のRRが高かった。
- Signal event であったドイツでのSMR より一桁低かった（almost an order of magnitude lower）。
- つまり、新たな”signal”となる結果は得られなかった。
- Hexavac のRR が高いのは、接種後7日以内の群と、1回目の接種の群である。→最もSUDが起こりやすい年齢群に相当することと、risk-period とcontrol-period がSUDのbasal ratesに影響をうけることを考えると、年齢に関係する「調整されていない交絡因子」の影響の可能性がある。

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A modified self-controlled case series method to examine association between multidose vaccinations and death

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7. Conclusion

The standard SCCS method is not suitable for the analysis of a possible association of death after multiple dose vaccinations. For this special situation, two methods have been developed on the basis of the standard SCCS method. In the first method, observation periods are truncated according to the vaccination schedule. The second method for censored, perturbed, or curtailed post-event exposures was proposed by Farrington *et al.* [8] and works by introducing a correction term in the formula. Simulation studies in a specific setting with short risk periods show that the two methods provide comparable and precise estimates under the assumption that infants are vaccinated in accordance with recommended vaccination schedules.

The major advantage of the proposed SCCS method with truncated observation periods is its appealing simplicity. It can be applied without special programming, within the same framework as the standard case series method. Its major disadvantage is that it requires that successive vaccine doses are separated by a known minimum time-interval. This is not an unduly restrictive requirement for studies of multidose vaccines, provided that the risk period of interest is short relative to this interval.

The SCCS method with correction factor is more complicated to apply, but makes no assumption about separations between doses. The simulations undertaken here, with short risk periods, suggest that it is marginally more efficient than the method with truncated observation periods, and tends to have slighly better α-error.

In conclusion, the SCCS method with truncated observation periods is an attractive alternative. Its properties require further investigation in more general contexts, in particular when risk periods are longer than those considered here. This is the topic of ongoing further work.

まとめ

- SCCSはcase control studyを補完することができる（最近ではmodified SCCSが提唱されているが、まだ検証段階といえる）。
- Case control study でリクルートされたcase のみを解析対象とする。
- 本事業でも実施可能。
- 最もCriticalなデータは、予防接種歴（種類、接種日）である。