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Preliminary evaluation of aluminum content in childhood vaccines and risk of asthma in a Danish nationwide cohort

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Study cohort

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- Born in Denmark 2009-2016
- Study start 1/1 2011; study end 12/31 2018
- Follow-up from 2 to 5-years-of-age
- Exposure and outcome data from nationwide-registers
- N=470,477 children

The Danish schedule

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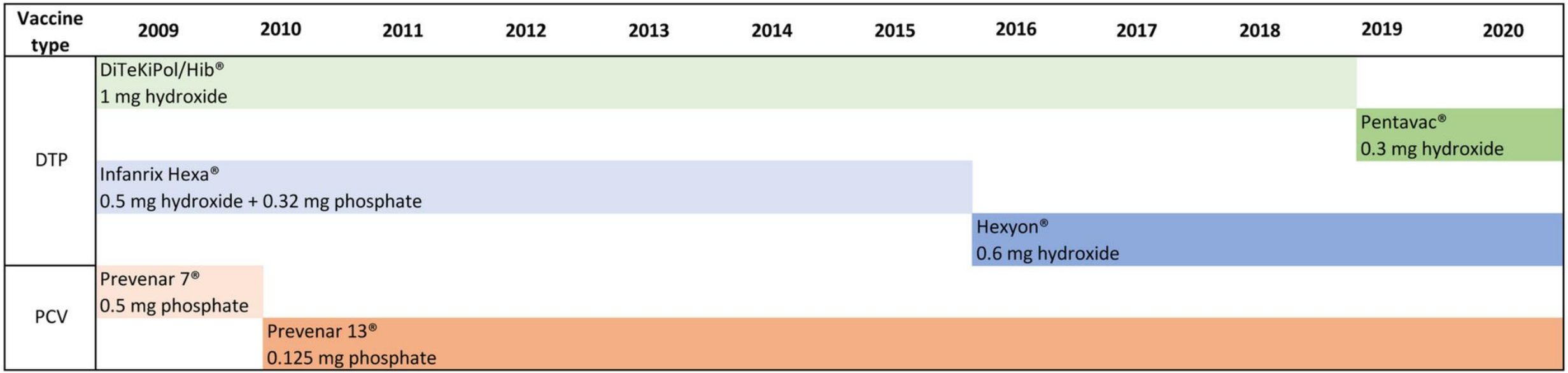
Danish schedule

3 mo.: DiTePeIPVHib1 + PCV1
5 mo.: DiTePeIPVHib2 + PCV2
12 mo.: DiTePeIPVHib3 + PCV3
15 mo.: MMR1
4 yrs: MMR2
5 yrs: DiTePeIPV booster
12 yrs: HPV1 and HPV2



Cumulative aluminium exposure

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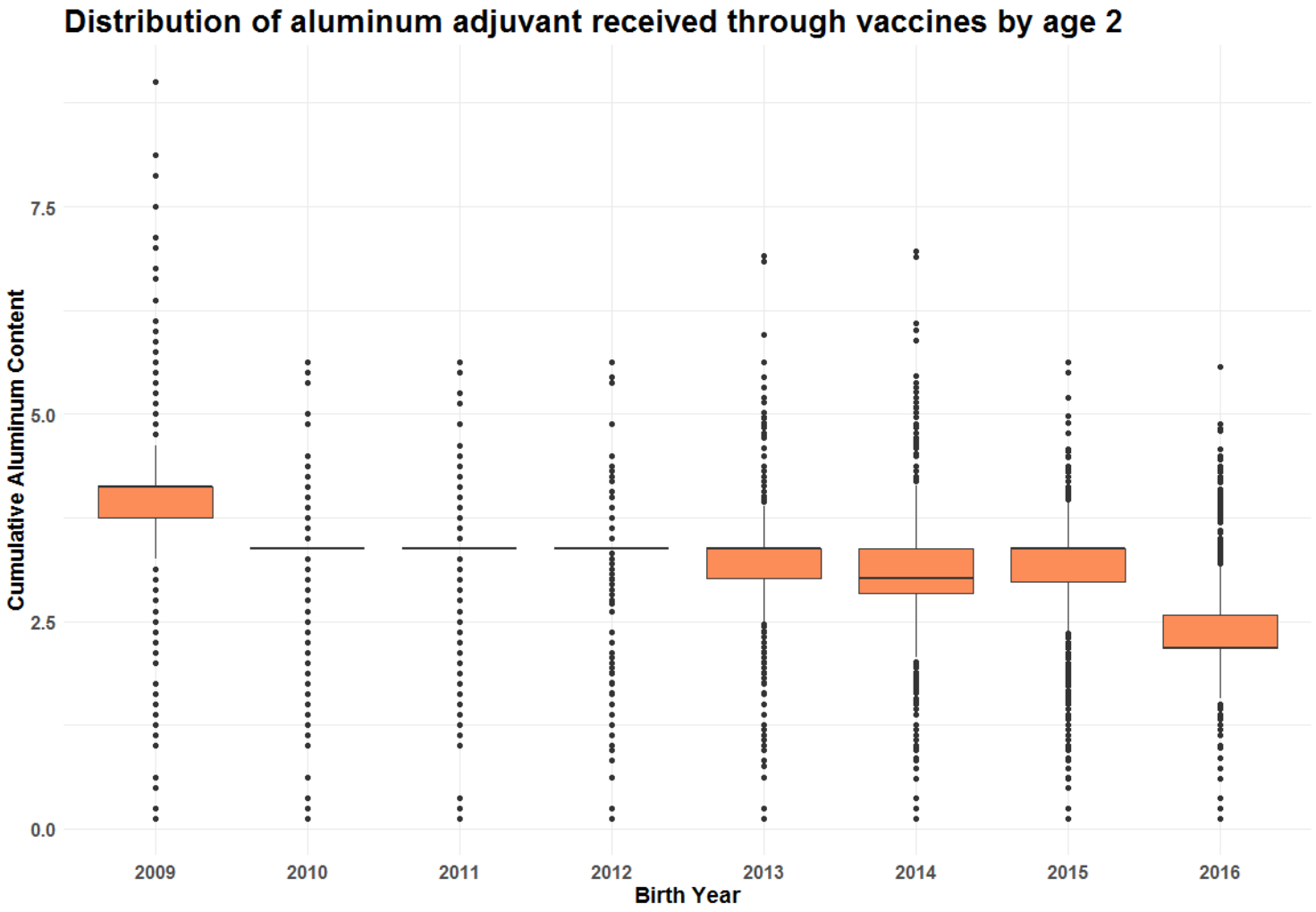

Summary statistics of cumulative aluminum adjuvant by age 2

Birth Year	Median (50%)	1st Quartile (25%)	3rd Quartile (75%)
2009	4.125	3.750	4.125
2010	3.375	3.375	3.375
2011	3.375	3.375	3.375
2012	3.375	3.375	3.375
2013	3.375	3.015	3.375
2014	3.015	2.835	3.375
2015	3.375	2.975	3.375
2016	2.175	2.175	2.575

Asthma outcome definitions

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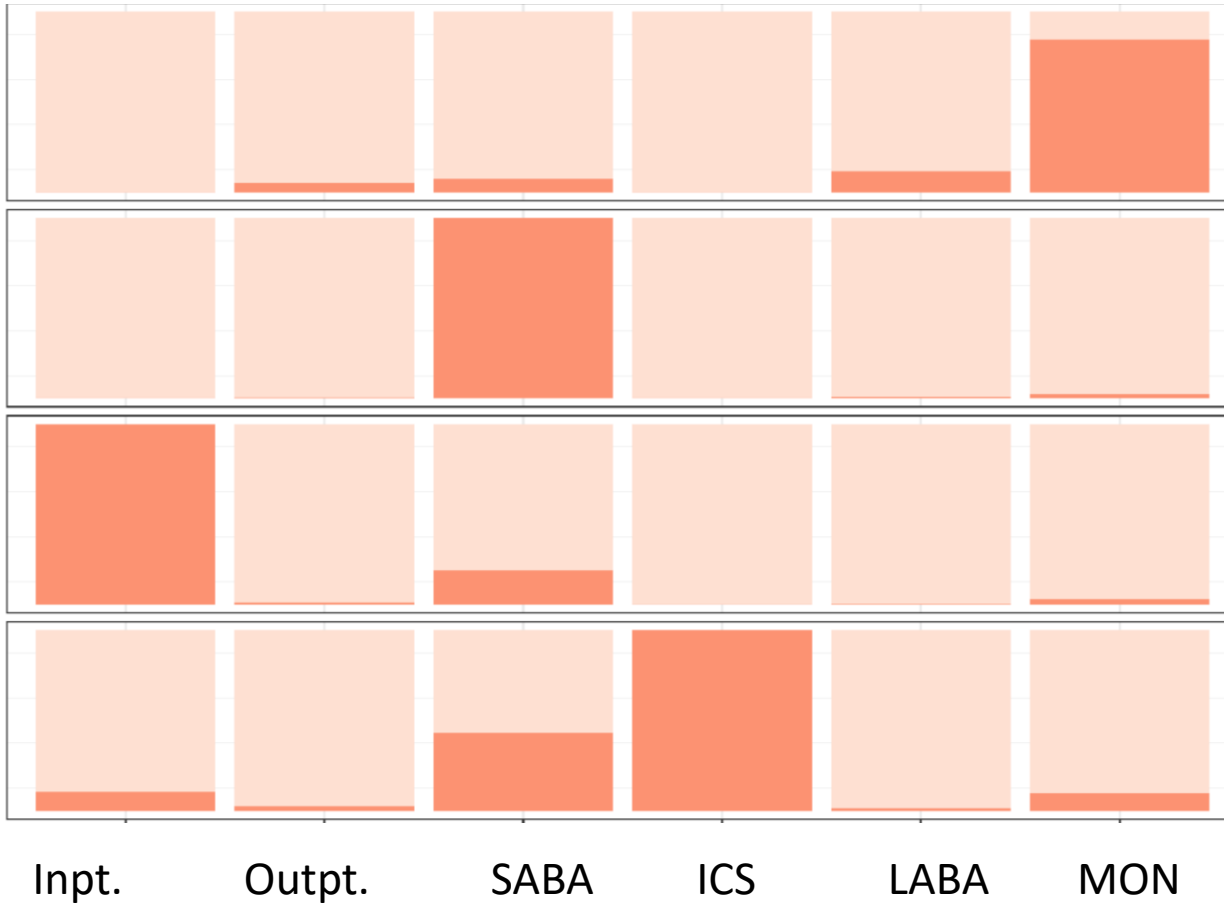
- Hospital contacts, ICD-10 J45 (asthma), J46 (status asthmaticus), in- and outpatients
- Community anti-asthmatics prescriptions: Inhaled corticosteroids (n=2), short-acting beta-agonists (n=3), montelukast (n=2), long-acting beta-agonists (n=1)
- Primary outcome: Hospitalization and/or anti-asthma drug use
- Exclusion criteria: Any prescriptions or hospitalizations before the age of 2.
- Date of outcome: First among the above events

Secondary outcomes - latent class analysis



Cluster 1: ”Montelukast”
6.5%

Cluster 2: ”SABA”
23.3%

Cluster 3: ”Hospitalization”
7.9%

Cluster 4: ”Inhaled corticosteroids +/- SABA”
62.3%

SABA: Short-acting beta agonist; LABA: Long-acting beta agonist; ICS: Inhaled corticosteroid; MON: Montelukast.

Cohort characteristics

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Cumulative aluminum received by 2-yrs-of-age

	<2.25mg (N=52221)	0 mg (N=5767)	2.25mg (N=31034)	>2.25mg-<3.375mg (N=94776)	3.375mg (N=229016)	>3.375mg (N=57663)	Overall (N=470477)
BYEAR							
2009	1760 (3.4%)	771 (13.4%)	752 (2.4%)	7591 (8.0%)	1324 (0.6%)	49956 (86.6%)	62154 (13.2%)
2010	1577 (3.0%)	680 (11.8%)	6470 (20.8%)	3552 (3.7%)	49378 (21.6%)	1032 (1.8%)	62689 (13.3%)
2011	1318 (2.5%)	637 (11.0%)	5629 (18.1%)	2985 (3.1%)	46972 (20.5%)	835 (1.4%)	58376 (12.4%)
2012	1261 (2.4%)	621 (10.8%)	5423 (17.5%)	2881 (3.0%)	46447 (20.3%)	661 (1.1%)	57294 (12.2%)
2013	3151 (6.0%)	733 (12.7%)	3798 (12.2%)	18832 (19.9%)	27667 (12.1%)	1149 (2.0%)	55330 (11.8%)
2014	6940 (13.3%)	719 (12.5%)	2300 (7.4%)	31041 (32.8%)	13222 (5.8%)	1941 (3.4%)	56163 (11.9%)
2015	4621 (8.8%)	776 (13.5%)	5122 (16.5%)	8050 (8.5%)	37852 (16.5%)	1089 (1.9%)	57510 (12.2%)
2016	31593 (60.5%)	830 (14.4%)	1540 (5.0%)	19844 (20.9%)	6154 (2.7%)	1000 (1.7%)	60961 (13.0%)
KOEN							
Boys	26964 (51.6%)	2975 (51.6%)	16132 (52.0%)	48821 (51.5%)	116904 (51.0%)	29584 (51.3%)	241380 (51.3%)
Girls	25257 (48.4%)	2792 (48.4%)	14902 (48.0%)	45955 (48.5%)	112112 (49.0%)	28079 (48.7%)	229097 (48.7%)
MMRby2							
No MMR vaccination by 2 yrs of age	10324 (19.8%)	5288 (91.7%)	8913 (28.7%)	11254 (11.9%)	24439 (10.7%)	6609 (11.5%)	66827 (14.2%)
MMR vaccination by 2 yrs of age	41897 (80.2%)	479 (8.3%)	22121 (71.3%)	83522 (88.1%)	204577 (89.3%)	51054 (88.5%)	403650 (85.8%)
OPR							
Denmark	44773 (85.7%)	4378 (75.9%)	26830 (86.5%)	83990 (88.6%)	206393 (90.1%)	52622 (91.3%)	418986 (89.1%)
Western country	1615 (3.1%)	402 (7.0%)	861 (2.8%)	2576 (2.7%)	5079 (2.2%)	878 (1.5%)	11411 (2.4%)
Non-Western Country	5833 (11.2%)	987 (17.1%)	3343 (10.8%)	8210 (8.7%)	17544 (7.7%)	4163 (7.2%)	40080 (8.5%)

KOEN: Sex; OPR: Mothers country of origin.

Main Results – Hosp. or anti-asthma medication

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Table: Association between cumulative aluminum received through vaccines by age 2 and asthma by age 5 among 470477 Danish children born 2009 to 2016 and followed 2011 to 2018

Aluminum	Asthma cases[1]	Person-years of follow-up	Hazard ratio (95% CIs)[2]
0 mg	62	13,082.00	0.90 (0.68 to 1.19)
<2.25mg	327	65,167.16	1.00 (- to -)
2.25mg	446	78,643.45	1.07 (0.92 to 1.24)
>2.25mg-<3.375mg	1092	206,053.42	1.00 (0.88 to 1.14)
3.375mg	3096	597,727.75	0.98 (0.86 to 1.11)
>3.375mg	838	165,528.63	1.00 (0.84 to 1.18)

[1]Hospitalization and/or anti-asthma prescription drug use

[2]Adjusted for sex, year of birth, maternal country of origin, and MMR vaccination by age 2.

Main Results – Dose-response

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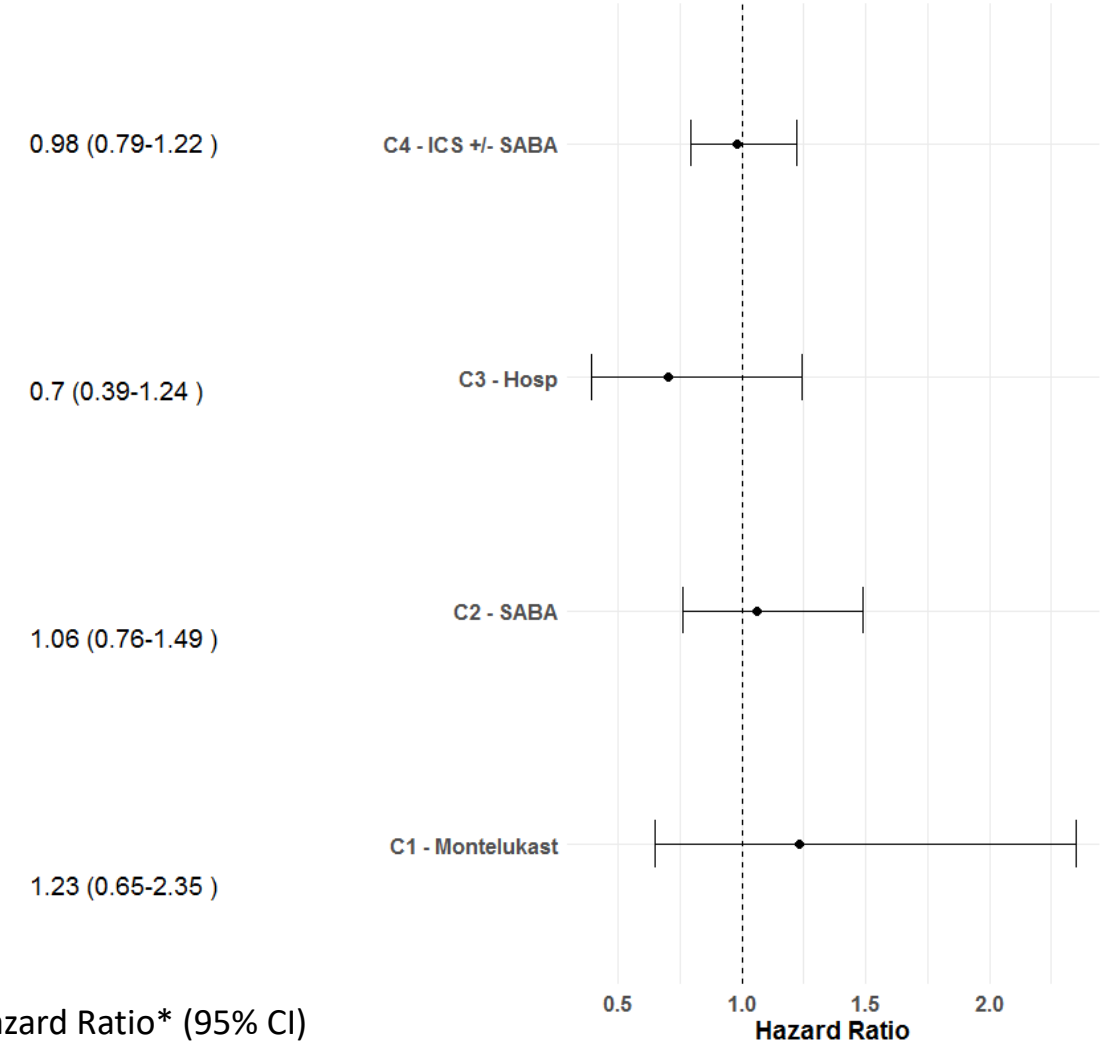
Table: Dose-response (per 1 mcg) association between cumulative aluminum received through vaccines by age 2 and asthma by age 5

	Hazard ratio (95% CIs)
cumALU:BYEAR2009	0.92 (0.84 to 1.01)
cumALU:BYEAR2010	0.91 (0.81 to 1.03)
cumALU:BYEAR2011	1.03 (0.90 to 1.19)
cumALU:BYEAR2012	0.97 (0.85 to 1.12)
cumALU:BYEAR2013	1.01 (0.88 to 1.15)
cumALU:BYEAR2014	1.07 (0.93 to 1.23)
cumALU:BYEAR2015	0.95 (0.79 to 1.15)
cumALU:BYEAR2016	1.11 (0.83 to 1.50)

Association between aluminum and asthma clusters



Hazard Ratio* (95% CI)

Comparing >3.375mg cumulative aluminum received through vaccines by 2-yrs-of-age to <2.25mg

* Adjusted for sex, year of birth, maternal country of origin, MMR vax before 2-yrs-of-age

Limitations

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- Limited variability in cumulative aluminum

- Validity of using asthma diagnosis and anti-asthma drug use before 5-yrs-of-age

Take-away

- No support for an association between aluminium in vaccines and asthma by 5-yrs-of-age in Denmark