



The association between COVID-19 vaccines and bullous pemphigoid: a case-control study

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Outline

- Background.
- Methods.
- Results.
- Discussion.
- Conclusions.



Background and rationale

Bullous pemphigoid and COVID-19 vaccines



Bullous pemphigoid (BP)

- Most common autoimmune blistering skin disease.
- Symptoms: itching and blisters of the skin.
- Rare condition (median age 80 yrs), increasing incidence, high mortality.
- Cause unknown.
- Systematic reviews and population-based studies found gliptins, loop diuretics and other drugs to be associated with BP.[1-2]



Images shared by Dr Sophie Leducq



Background 1/2

- Fast development of the COVID-19 vaccine and early rollout prevented approx. 14 millions of deaths worldwide within the first year since the start of the UK vaccination programme.
- Vaccine hesitancy was one of the most important barrier to population immunity. There is a concern about adverse effects.



Background 2/2

- Case reports/series show cases of bullous pemphigoid (BP) after COVID-19 vaccines.
- No population-based study in the UK investigated the association between the COVID-19 vaccines and BP.
- The only population-based study on vaccines and BP showed no association between COVID-19 vaccines and BP[1] but used a database from specialised hospitals which were not representative of the general population in their respective countries and the UK.



Aim and rationale

- To provide important and precise estimates of the associations between COVID-19 vaccines and BP for the whole UK.
- To support MHRA, GPs, and other healthcare professionals in decision making regarding the choice of the COVID-19 vaccines and to reduce the vaccine hesitancy.



Methods



Methods

- Study design: nested case-control 2021-2023.
- Outcome: incident cases of BP (18 years or older).
- Controls: up to 4 controls per BP case matched by age, sex and GP practice.
- Exposure: COVID-19 vaccination (3 months before index the date, i.e., BP diagnosis/pseudo-diagnosis).
- Analysis: conditional logistic regression to calculate crude/partially adjusted/adjusted odds ratios (OR) for exposure to COVID-19 vaccines, in general, and by vaccine product, type and number of doses.
- Databases: Clinical Practice Research Datalink (CPRD) GOLD (Vision, UK) and Aurum (EMIS, England only).



Types of exposures

- General: COVID-19 vaccine.
- Number of doses before the index date:
 - 0,1,2, ≥ 3 (doses recommended for healthy adults: 2 + Omicron booster).
- Product: Pfizer, Spikevax, AstraZeneca
- Type: mRNA, vector



Main analysis

Crude: COVID-19 vaccines ~ BP.

- Confounders[1-4]:
 - Adjusted *a priori* in all analyses: Dementia, Parkinson's disease, and stroke.
 - Determined by analysis:
 - Diabetes, Multiple Sclerosis, Epilepsy, Rheumatoid Arthritis, Severe Mental Illness (Schizophrenia, affective disorder, and other) diagnosed at least one year before index date, and SARS-CoV-2 within one year before index date.
 - All confounders previously associated with BP and affected the number of vaccine doses a patient takes according to the Green Book (at risk groups, and delay in vaccination due to recovery from COVID-19).
 - Condition was considered a confounder if OR > 10% and the confounder is associated with exposure and outcome.
- Fully adjusted analysis: each vaccine exposure adjusted separately for:
 - Drugs previously associated with BP: gliptins, antidementia, and antiepileptic drugs (latest prescription within one year before index date).[5]
 - Anti-inflammatory drugs used to treat BP and other conditions: azathioprine, dapsone, doxycycline, prednisolone, methotrexate, mycophenolate, rituximab, and dupilumab (latest prescription within three months before index date).[6]
 - Confounders if the OR in the confounder analysis changed by more than 10% and the result was statistically significant.
- OR > 2: strong association, $p < 0.005$ statistically significant result after Bonferroni correction.

1. UK Health Security Agency. COVID-19: the green book, chapter 14a. In: UK Health Security Agency, ed. The Green Book. 2024 ed. GOV.UK; 2020:chap 14a. Accessed 16/10/2024.

<https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a>

2. Försti AK, Jokelainen J, Ansakorpi H, et al. Psychiatric and neurological disorders are associated with bullous pemphigoid - a nationwide Finnish Care Register study. *Sci Rep-Uk*. Nov 15 2016;6doi:ARTN 37125 10.1038/srep37125

3. Kibsgaard L, Rasmussen M, Lamberg A, Deleuran M, Olesen AB, Vestergaard C. Increased frequency of multiple sclerosis among patients with bullous pemphigoid: a population-based cohort study on comorbidities anchored around the diagnosis of bullous pemphigoid. *Brit J Dermatol*. Jun 2017;176(6):1486-1491. doi:10.1111/bjd.15405

4. Christensen DM, Strange JE, Gislason G, et al. Charlson Comorbidity Index Score and Risk of Severe Outcome and Death in Danish COVID-19 Patients. *Journal of General Internal Medicine*. Sep 2020;35(9):2801-2803. doi:10.1007/s11606-020-05991-z

5. Swiderski M, Vinogradova Y, Knaggs RD, et al. The association between drugs and vaccines commonly prescribed to older people and bullous pemphigoid: a case-control study. *Brit J Dermatol*. 2024;doi:10.1093/bjd/ljae416

6. Borradori L, Van Beek N, Feliciani C, Tedbirt B, Antiga E, Bergman R, et al. Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV). *J Eur Acad Dermatol*. 2022;36(10):1689-704.



Subgroup and sensitivity analyses

- Subgroup analysis by Charlson Comorbidity Index (CCI) scores:
 - The risk of COVID-19 complications and mortality increases with each unit of CCI and is the highest when $CCI \geq 3$.
 - Therefore, we divided the study population by 0-2, and ≥ 3 CCI scores and ran the whole analysis for each study population subgroup.
- Analysis which restricts the exposure window to two months before index date to account for temporal delay in vaccination exposure.
- Analysis which adjusted for the ethnicity Index of Multiple Deprivation (IMD) *a priori* in every model to account for inequalities in the COVID-19 vaccination access.

[1] Kim DH, Park HC, Cho A, et al. Age-adjusted Charlson comorbidity index score is the best predictor for severe clinical outcome in the hospitalized patients with COVID-19 infection. *Medicine*. May 7 2021;100(18)doi:ARTN e25900 10.1097/MD.00000000000025900

[2] Dolby T, Finning K, Baker A, et al. Monitoring sociodemographic inequality in COVID-19 vaccination uptake in England: a national linked data study. *J Epidemiol Commun H*. Jul 2022;76(7):646-652. doi:10.1136/jech-2021-218415



Results

Study population characteristics

Total, N = 13 895	Cases, N = 2828	Controls, N = 11 067
Characteristic	Cases N (%) ^a	Controls N (%) ^a
Sex		
Male	1401 (49.54)	5475 (49.47)
Female	1427 (50.46)	5592 (50.53)
Median age (IQR)	80 (72-86)	79 (71-85)
Age		
<60	279 (9.87)	1116 (10.08)
60-69	325 (11.49)	1300 (11.75)
70-79	807 (28.54)	3217 (29.07)
80-89	1047 (37.02)	4139 (37.40)
>=90	370 (13.08)	1295 (11.70)
Comorbidities		
Dementia	286 (10.11)	492 (4.45)
Parkinson's disease	67 (2.37)	107 (0.97)
Stroke	401 (14.18)	1216 (10.99)
Diabetes	874 (30.91)	2384 (21.54)
Multiple Sclerosis	36 (1.27)	36 (0.33)
Epilepsy	80 (2.83)	155 (1.40)
Rheumatoid Arthritis	76 (2.69)	215 (1.94)
Severe Mental Illness	50 (1.77)	120 (1.08)
SARS-CoV-2	126 (4.46)	335 (3.03)

a - percentages might not total 100%

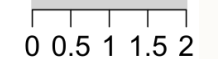
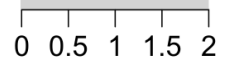
Total, N = 13 895	Cases, N = 2828	Controls, N = 11 067
Characteristic	Cases N (%) ^a	Controls N (%) ^a
Charlson Comorbidity Index		
0	865 (30.59)	4742 (42.85)
1	497 (17.57)	1764 (15.94)
2	477 (16.87)	1785 (16.13)
>=3	989 (34.97)	2776 (25.08)
Ethnicity		
Asian	147 (5.20)	435 (3.93)
Black	40 (1.41)	160 (1.45)
White	2087 (73.80)	7976 (72.07)
Other	32 (1.13)	97 (0.88)
Unknown	522 (18.46)	2399 (21.68)
Index of Multiple Deprivation		
1 (most affluent)	444 (15.70)	1795 (16.22)
2	448 (15.84)	1621 (14.65)
3	392 (13.86)	1521 (13.74)
4	328 (11.60)	1221 (11.03)
5 (most deprived)	262 (9.26)	959 (8.67)
Unknown	954 (33.73)	3950 (35.69)

a - percentages might not total 100%



Main analysis

Exposure (a)	Cases, n (%)	Controls, n (%)	Crude (c)		Fully adjusted (c,d)	
			OR (95% CI)	p (b)	OR (95% CI)	p (b)
General						
Vaccine (GOLD and Aurum)	1157 (40.91)	4668 (42.18)	0.89 (0.79-1.01)	0.07	0.92 (0.81-1.05)	0.2
Vaccine (GOLD)	163 (36.63)	647 (37.18)	0.96 (0.69-1.34)	0.81		
Vaccine (Aurum)	994 (41.71)	4021 (43.11)	0.89 (0.78-1.01)	0.07		
Doses (GOLD and Aurum) (e)						
1	252 (8.91)	935 (8.45)	0.70 (0.45-1.10)	0.12	0.69 (0.43-1.10)	0.12
2	627 (22.17)	2393 (21.62)	0.57 (0.36-0.90)	0.02	0.54 (0.33-0.88)	0.01
>=3	1851 (65.45)	7403 (66.89)	0.47 (0.29-0.76)	<0.005	0.48 (0.29-0.79)	<0.005
Vaccine products (Aurum)						
AstraZeneca	216 (9.06)	712 (7.63)	1.17 (0.88-1.55)	0.28	1.14 (0.84-1.55)	0.4
Pfizer	335 (14.06)	1526 (16.36)	0.77 (0.63-0.94)	0.01	0.78 (0.63-0.98)	0.03
Spikevax	94 (3.94)	358 (3.84)	0.93 (0.69-1.25)	0.63	0.94 (0.69-1.30)	0.73
Vaccine types (Aurum)						
mRNA (Pfizer, Spikevax)	429 (18.00)	1884 (20.20)	0.82 (0.68-0.98)	0.03	0.83 (0.68-1.02)	0.07
Vector (AstraZeneca)	216 (9.06)	712 (7.63)	1.22 (0.92-1.61)	0.16	1.19 (0.88-1.61)	0.26



a - Not vaccinated was the baseline category. Exposure was defined as latest COVID-19 vaccination within three months prior to BP diagnosis.

The exposure in the doses category was defined as the number of doses prior to BP diagnosis.

b - statistically significant results when $p < 0.005$.

c - adjusted a priori for dementia, Parkinson's disease and stroke.

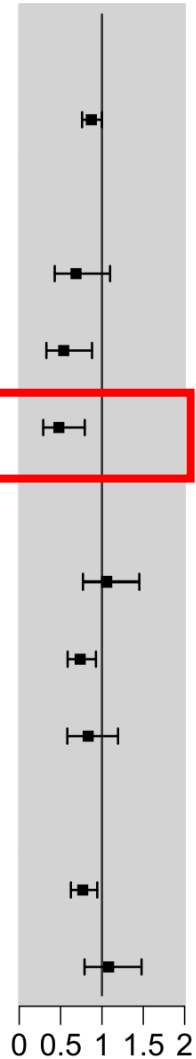
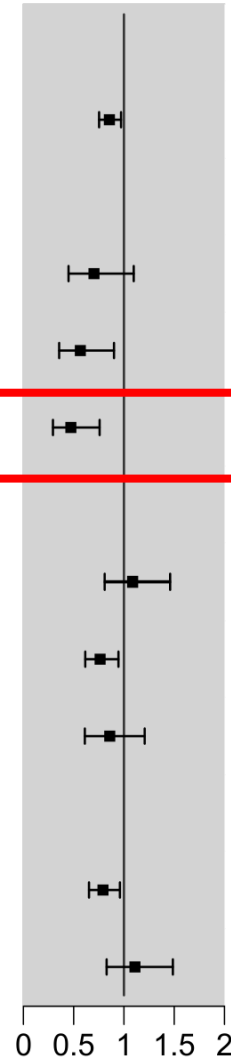
d - additionally adjusted for gliptins, antiepileptic drugs, azathioprine, dapsone, doxycycline, prednisolone, methotrexate, mycophenolate, dupilumab.

e - additionally adjusted for the multiple sclerosis and SARS-CoV-2 diagnoses in the fully adjusted analysis.



Two-month exposure window

Exposure (a)	Cases, n (%)	Controls, n (%)	Crude (c)		Fully adjusted (c,d)		
			OR (95% CI)	p (b)	OR (95% CI)	p (b)	
General (GOLD and Aurum)							
Vaccine	771 (27.26)	3208 (28.99)	0.85 (0.75-0.97)	0.02	0.87 (0.76-1.00)	0.05	
Doses (GOLD and Aurum) (e)							
1	252 (8.91)	935 (8.45)	0.70 (0.45-1.10)	0.12	0.69 (0.43-1.10)	0.12	
2	627 (22.17)	2393 (21.62)	0.57 (0.36-0.90)	0.02	0.54 (0.33-0.88)	0.01	
>=3	1851 (65.45)	7403 (66.89)	0.47 (0.29-0.76)	<0.005	0.48 (0.29-0.79)	<0.005	
Vaccine products (Aurum)							
AstraZeneca	145 (6.08)	493 (5.29)	1.09 (0.81-1.46)	0.58	1.06 (0.77-1.45)	0.73	
Pfizer	218 (9.15)	1012 (10.85)	0.76 (0.62-0.95)	0.01	0.74 (0.59-0.93)	0.01	
Spikevax	60 (2.52)	249 (2.67)	0.86 (0.61-1.21)	0.38	0.83 (0.58-1.19)	0.32	
Vaccine types (Aurum)							
mRNA (Pfizer, Spikevax)	278 (11.67)	1261 (13.52)	0.79 (0.65-0.96)	0.02	0.77 (0.62-0.94)	0.01	
Vector (AstraZeneca)	145 (6.08)	493 (5.29)	1.11 (0.83-1.49)	0.49	1.08 (0.79-1.48)	0.63	



a - Not vaccinated was the baseline category. Exposure was defined as latest COVID-19 vaccination within two months prior to BP diagnosis.

The exposure in the doses category was defined as the number of doses prior to BP diagnosis.

b - statistically significant results when p<0.005.

c - adjusted a priori for dementia, Parkinson's disease and stroke.

d - additionally adjusted for gliptins, antiepileptic drugs, azathioprine, dapson, doxycycline, prednisolone, methotrexate, mycophenolate, dupilumab.

e - additionally adjusted for the multiple sclerosis and SARS-CoV-2 diagnoses in the fully adjusted analysis.



Subgroup analysis

Charlson Comorbidity Index 0-2

Exposure (a)	Cases, n (%)	Controls, n (%)	Crude (c)		Fully adjusted (c,d)	
			OR (95% CI)	p (b)	OR (95% CI)	p (b)
General (GOLD and Aurum)						
Vaccine	713 (39.44)	2221 (39.24)	0.95 (0.81-1.11)	0.51	0.99 (0.83-1.18)	0.89
Doses (GOLD and Aurum) (e)						
1	160 (8.85)	463 (8.18)	0.74 (0.43-1.26)	0.26	0.63 (0.36-1.10)	0.11
2	403 (22.29)	1243 (21.96)	0.54 (0.31-0.95)	0.03	0.48 (0.27-0.87)	0.02
>=3	1173 (64.88)	3738 (66.04)	0.43 (0.24-0.76)	<0.005	0.42 (0.23-0.77)	<0.005
Vaccine products (Aurum)						
AstraZeneca	144 (9.56)	400 (8.55)	1.15 (0.79-1.67)	0.46	1.22 (0.82-1.82)	0.33
Pfizer	199 (13.21)	733 (15.67)	0.69 (0.53-0.91)	0.01	0.76 (0.57-1.02)	0.07
Spikevax	53 (3.52)	148 (3.16)	0.95 (0.64-1.42)	0.81	1.07 (0.68-1.66)	0.78
Vaccine types (Aurum)						
mRNA (Pfizer, Spikevax)	252 (16.72)	881 (18.83)	0.75 (0.58-0.96)	0.02	0.83 (0.63-1.08)	0.16
Vector (AstraZeneca)	144 (9.56)	400 (8.55)	1.21 (0.84-1.75)	0.31	1.28 (0.86-1.89)	0.22

a - Not vaccinated was the baseline category. Exposure was defined as latest COVID-19 vaccination within three months prior to BP diagnosis.

The exposure in the doses category was defined as the number of doses prior to BP diagnosis.

b - statistically significant results when $p < 0.005$.

c - adjusted a priori for dementia, Parkinson's disease and stroke.

d - additionally adjusted for gliptins, antiepileptic drugs, azathioprine, dapsons, doxycycline, prednisolone, methotrexate, mycophenolate, dupilumab.

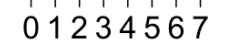
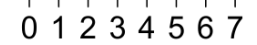
e - additionally adjusted for the diabetes diagnosis in the fully adjusted analysis.



Subgroup analysis

Charlson Comorbidity Index ≥ 3

Exposure (a)	Cases, n (%)	Controls, n (%)	Crude (c)		Fully adjusted (c,d)	
			OR (95% CI)	p (b)	OR (95% CI)	p (b)
General (GOLD and Aurum)						
Vaccine	327 (45.61)	566 (46.82)	0.97 (0.75-1.27)	0.84	0.99 (0.74-1.32)	0.94
Doses (GOLD and Aurum)						
1	66 (9.21)	112 (9.26)	1.06 (0.30-3.72)	0.93	1.37 (0.33-5.61)	0.67
2	155 (21.62)	259 (21.42)	1.11 (0.30-4.01)	0.88	1.41 (0.32-6.13)	0.65
>=3	481 (67.09)	817 (67.58)	0.93 (0.25-3.44)	0.92	1.20 (0.27-5.31)	0.81
Vaccine products (Aurum)						
AstraZeneca	53 (8.49)	73 (6.89)	1.25 (0.66-2.39)	0.49	1.12 (0.55-2.29)	0.75
Pfizer	101 (16.19)	184 (17.37)	0.94 (0.62-1.44)	0.79	0.77 (0.48-1.23)	0.27
Spikevax	28 (4.49)	64 (6.04)	0.64 (0.35-1.18)	0.15	0.62 (0.33-1.20)	0.16
Vaccine types (Aurum)						
mRNA (Pfizer, Spikevax)	129 (20.67)	248 (23.42)	0.88 (0.59-1.30)	0.51	0.74 (0.48-1.14)	0.17
Vector (AstraZeneca)	53 (8.49)	73 (6.89)	1.24 (0.65-2.36)	0.52	1.14 (0.56-2.33)	0.72



a - Not vaccinated was the baseline category. Exposure was defined as latest COVID-19 vaccination within three months prior to BP diagnosis. The exposure in the doses category was defined as the number of doses prior to BP diagnosis.

b - statistically significant results when $p < 0.005$.

c - adjusted a priori for dementia, Parkinson's disease and stroke.

d - additionally adjusted for gliptins, antiepileptic drugs, azathioprine, dapsone, doxycycline, prednisolone, methotrexate, mycophenolate, dupilumab.



Adjusted for ethnicity and IMD

Exposure (a)	Cases, n (%)	Controls, n (%)	Crude (c)		Fully adjusted (c,d)		
			OR (95% CI)	p (b)	OR (95% CI)	p (b)	
General (GOLD and Aurum)							
Vaccine	1157 (40.91)	4668 (42.18)	0.90 (0.80–1.01)	0.08		0.92 (0.81–1.05)	0.22
Doses (GOLD and Aurum)							
1	252 (8.91)	935 (8.45)	0.70 (0.44–1.09)	0.11		0.66 (0.41–1.05)	0.08
2	627 (22.17)	2393 (21.62)	0.56 (0.35–0.89)	0.01		0.51 (0.31–0.84)	0.01
>=3	1851 (65.45)	7403 (66.89)	0.47 (0.29–0.76)	<0.005		0.47 (0.29–0.78)	<0.005
Vaccine products (Aurum)							
AstraZeneca	216 (9.06)	712 (7.63)	1.18 (0.89–1.57)	0.26		1.16 (0.85–1.57)	0.36
Pfizer	335 (14.06)	1526 (16.36)	0.77 (0.63–0.95)	0.01		0.79 (0.63–0.98)	0.03
Spikevax	94 (3.94)	358 (3.84)	0.93 (0.69–1.26)	0.66		0.95 (0.69–1.31)	0.76
Vaccine types (Aurum)							
mRNA (Pfizer, Spikevax)	429 (18.00)	1884 (20.20)	0.82 (0.68–0.99)	0.04		0.84 (0.69–1.02)	0.08
Vector (AstraZeneca)	216 (9.06)	712 (7.63)	1.23 (0.93–1.63)	0.15		1.20 (0.89–1.63)	0.23

a – Not vaccinated was the baseline category. Exposure was defined as latest COVID–19 vaccination within three months prior to BP diagnosis.

The exposure in the doses category was defined as the number of doses prior to BP diagnosis.

b – statistically significant results when p<0.005.

c – adjusted a priori for dementia, Parkinson's disease, stroke, Index of Multiple Deprivation, and ethnicity.

d – additionally adjusted for gliptins, antiepileptic drugs, azathioprine, dapsons, doxycycline, prednisolone, methotrexate, mycophenolate, dupilumab.



Discussion and Conclusions



Comparison with literature 1/2

- We compared our results with a population-based retrospective cohort study by Birabaharan et al., 2022
- Trinetx database – data collection period comprised mainly academic medical institutions (in/outpatient) in the United States only.
- Found no association between mRNA vaccines and BP:
 - **Risk Ratio: 0.77; 95%CI: 0.37-1.57.**
- The mRNA vaccines included Moderna (Spikevax) and Pfizer/BioNTech like in our study.
- We also found no association between mRNA vaccines and BP:
 - **Odds Ratio: 0.83; 95%CI: 0.68-1.02.**



Comparison with literature 2/2

- We compared our results with a population-based retrospective cohort study by Peng et al., 2023.
- Territory-wide medical records from Hong Kong Hospital Authority (hospital, general, and specialist outpatient clinics) and Department of Health vaccination data (Pfizer/BioNTech, Sinovac-CoronaVac [inactivated]).
- Found increased pemphigoid risk following COVID-19:
 - **Adjusted Hazard Ratio: 2.39; 95%CI: 1.83-3.11.**
- Simultaneously, the authors found a reduced pemphigoid risk following ≥ 2 vaccine doses:
 - **Adjusted Hazard Ratio: 0.45; 95%CI: 0.29-0.70**
- We found reduced BP risk following ≥ 2 vaccine doses:
 - **Odds Ratio: 0.48; 95%CI: 0.29-0.79.**
 - SARS-CoV-2 infection was a confounder for which we adjusted in our analysis.
- **Peng et al. suggest that COVID-19 vaccination could confer protection from infection-induced autoimmunity by reducing the severity of COVID-19.**



Strengths

- Large study population $N = 13\,895$, representative of the UK population.
- Analysis design based the selection of confounders and other covariates on the government's vaccination policy (Green Book) and previous studies on bullous pemphigoid.
- Sensitivity analyses (2-month exposure window, sociodemographic inequalities) found no differences in the estimates of the association between COVID-19 vaccines and BP.
- The results were similar to previous population-based studies.



Limitations

- We couldn't compare the results within the Charlson Comorbidity Index subgroup analysis, because the CCI ≥ 3 subgroup population was too small.
- There is a considerable percentage of missing Ethnicity and IMD data.
- The vaccination product and type data is only available in CPRD Aurum.



Conclusions

- No association between COVID-19 vaccines and increased BP risk was found.
- Reduced BP risk following three or more vaccine doses might be a potential protective effect against severe COVID-19 which could trigger BP.
- Future studies with more recent CPRD databases or other databases should look at differences between CCI and sociodemographic subgroups.



University of
Nottingham

UK | CHINA | MALAYSIA

Thank you