GP CME: Haematology Cases

October 2021

CASE 1

Scenario

- 52 year old European male
  - Fit and well
  - Brother recently diagnosed with diabetes
- PMHx
  - Nil
- Social Hx
  - Ex-smoker stopped 5 years ago (20 pack-year)
- Medication
  - Nil regular
  - NKDA

Continue

- Examination
  - Essentially normal
  - Mildly Elevated BMI 28
- Routine bloods
  - CBC, LFT, U&Es, HbA1c, cholesterol…etc

		Ref. Range
Haemoglobin	164	(130 – 175)
RBC	5.14	(4.30 – 6.00)
HCT	0.48	(0.30 – 0.44)
MCV	93	(80 – 99)
MCH	31.9	(27.0 – 33.0)
Platelets	188	(150 – 400)
WBC	13.1	(4.0 – 11.0)
Neutrophils	6.1	(1.90 – 7.5)
Lymphocytes	5.69	(1.00 – 4.00)
Monocytes	0.93	(0.20 – 1.00)
Eosinophils	0.32	(<0.51)
Basophils	0.05	(0.00 – 0.20)
Blood Film: Lymphocytosis with reactive lymphocyte morphology is suggestive of infection (especially viral). Suggest repeat in 4 – 6 weeks.		

CBC

	21/11/2016	13/02/2017	
Haemoglobin	164	165	(130 – 175)
RBC	5.14	5.15	(4.30 – 6.00)
HCT	0.48	0.49	(0.30 – 0.44)
MCV	93	95	(80 – 99)
MCH	31.9	32.0	(27.0 – 33.0)
Platelets	188	165	(150 – 400)
WBC	13.1	12.1	(4.0 – 11.0)
Neutrophils	6.1	5.17	(1.90 – 7.5)
Lymphocytes	5.69	5.79	(1.00 – 4.00)
Monocytes	0.93	0.85	(0.20 – 1.00)
Eosinophils	0.32	0.21	(<0.51)
Basophils	0.05	0.06	(0.00 – 0.20)

- Reactive lymphocytosis eg due to infection, inflammation, medication or autoimmune disorder should be considered first. If the lymphocytosis persists without an obvious clinical explanation then **an indolent lymphoproliferative disorder including Monoclonal B cell Lymphocytosis** can be considered. Suggest continue monitoring the lymphocyte count. **If the lymphocyte count is above 7 E+9/L, or if the patient has unexplained lymphadenopathy, hepatosplenomegaly or systemic symptoms of unexplained fever, night sweats or weight loss, then a cell marker study on the peripheral blood lymphocytes will be a useful initial test.**

Lymphocytosis

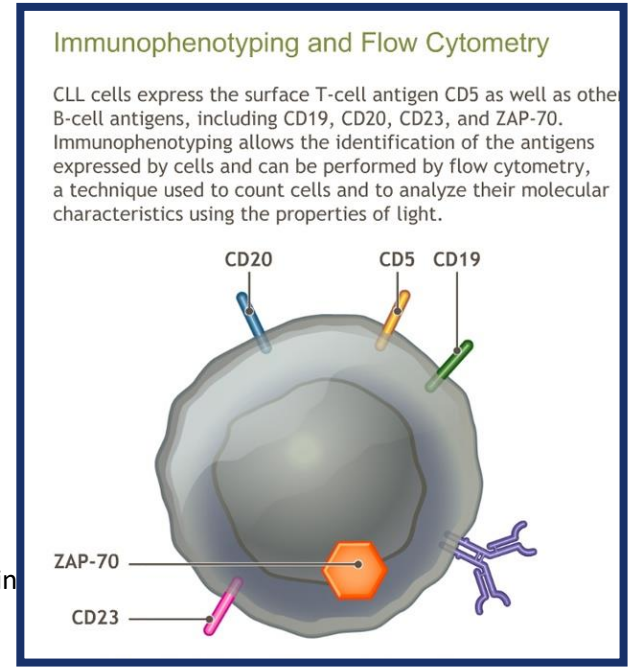
- Reactive
  - Infection
  - Medication
  - Autoimmune
  - Smoker (female)
  - “Stress”

- Clonal
  - Lymphoproliferative disorder
    - Lymphoma
    - Leukaemia
      - **Chronic lymphocytic leukaemia (CLL)**

CLL

- Epidemiology
  - Most common Leukaemia in Adult
  - Incidence 3 to 4 per 100,000 per year
  - Median age of onset ~67
  - Male > Female
  - 10% will have family history

- Diagnosis
  - 70% incidental finding on FBC
  - Requires ≥ $5x10^9$ circulating clonal **B-cells**
    - 3 month
    - Characteristic immunophenotype
      - CD5+, CD 23+, CD200+, weak CD20, weak surface immunoglobulin



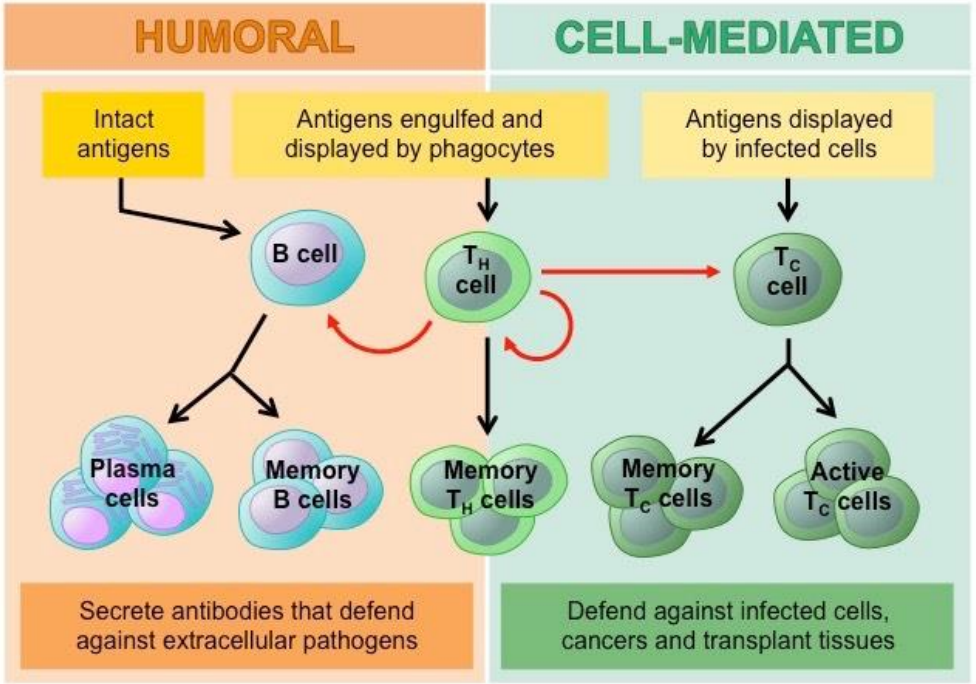
Management

- Key points
  - Indolent disease
  - Not curable but treatable
    - Therefore, most of these patient will be managed in primary care
      - Refer when requiring treatment
  - Monitoring
    - CBC
      - 6 monthly for a year and consider yearly if stable
    - Clinically
      - Lymphocyte count don’t necessary reflect severity of disease
  - Special consideration
    - Increase infection
      - Acquire hypogammoglobulinaemia
      - Annual flu vaccination
    - Increase risk of malignancy

Indication to Treat

1. Cytopenia attributed to CLL
    - Hb and platelet <100
2. Bulky lymphadenopathy
    - Splenomegaly (> 6cm below costal margin)
3. B symptoms
    - Fever, night sweats > 1 month
    - Weight loss > 10%
    - Fatigue (affecting daily activities)
4. Autoimmune disease
    - Autoimmune haemolytic anaemia or ITP
5. Progressive lymphocytosis (when baseline lymphocyte count is > $30x10^9$)
    - Lymphocyte doubling time < 6 month

Immune System



COVID Vaccination in CLL

CLINICAL TRIALS AND OBSERVATIONS

CME Article

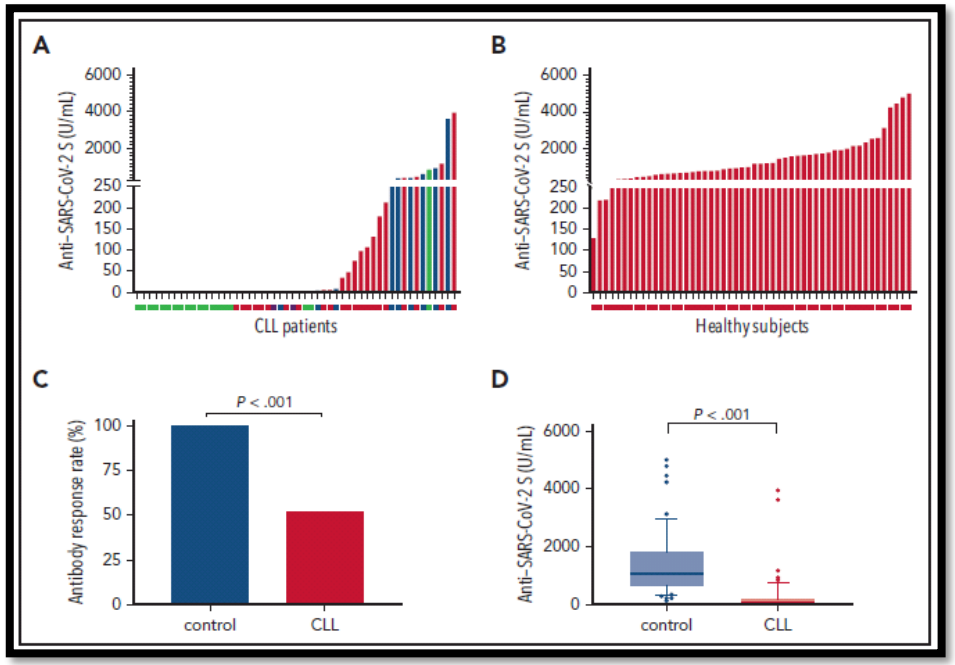
Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia

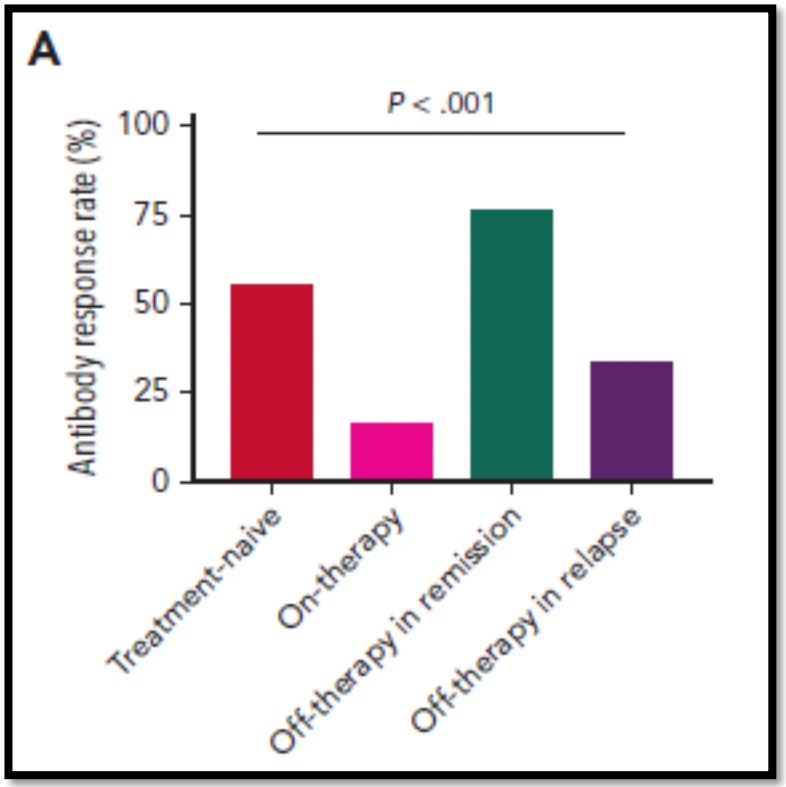
Yair Herishanu,[1,2,*] Irit Avivi,[1,2,*] Anat Aharon,[1,2] Gabi Shefer,[3] Shai Levi,[2] Yotam Bronstein,[1,2] Miguel Morales,[3] Tomer Ziv,[1] Yamit Shorer Arbel,[1] Lydia Scarfò,[4,5] Erel Joffe,[6] Chava Perry,[1,2] and Paolo Ghia[4,5]

[1]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [2]Department of Hematology and [3]Department of Endocrinology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [4]Division of Experimental Oncology, Università Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, Milan, Italy; [5]European Research Initiative on CLL (ERIC), Barcelona, Spain; and [6]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center–Weill Cornell College of Medicine, New York, NY

Blood. June 2021

Result


A
Anti–SARS-CoV-2 S (U/mL)
6000
4000
2000
250
200
150
100
50
0
CLL patients
B
Anti–SARS-CoV-2 S (U/mL)
6000
4000
2000
250
200
150
100
50
0
Healthy subjects
C
P < .001
Antibody response rate (%)
100
75
50
25
0
control
CLL
D
P < .001
Anti–SARS-CoV-2 S (U/mL)
6000
4000
2000
0
control
CLL


A
P < .001
Antibody response rate (%)
100
75
50
25
0
Treatment-naive
On-therapy
Off-therapy in remission
Off-therapy in relapse

The importance of B cell

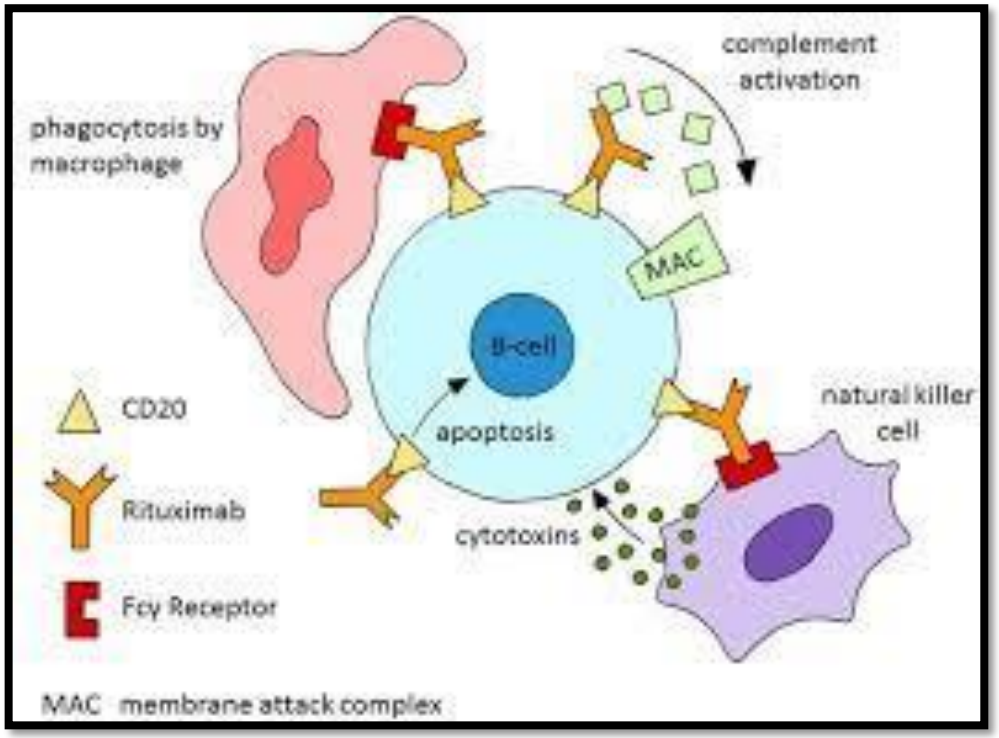
Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma

C. Perry,[1,2] E. Luttwak,[1,2] R. Balaban,[1] G. Shefer,[3] M. M. Morales,[3] A. Aharon,[1,2] Y. Tabib,[1] Y. C. Cohen,[1,2] N. Benyamini,[1,2] O. Beyar-Katz,[1,2] M. Neaman,[1,2] R. Vitkon,[1,2] N. Keren-Khadmy,[1] M. Levin,[1] Y. Herishanu,[1,2,*] and I. Avivi[1,2,*]

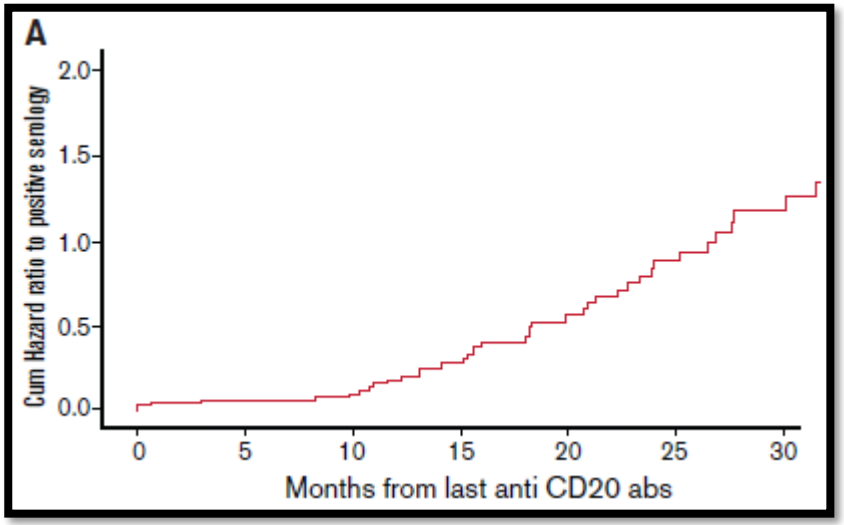
[1]Department of Hematology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and [3]Endocrinology Laboratory, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Blood Advances. Aug 21

Rituximab


complement activation
phagocytosis by macrophage
MAC
B-cell
apoptosis
natural killer cell
CD20
Rituximab
Fcγ Receptor
cytotoxins
MAC membrane attack complex

Anti-CD 20 Treatment



- Response 3-6 months
  - <10%
- Response >9 months
  - 80+%

1. Consumers with primary or acquired immunodeficiency states at the time of vaccination

1.1	Acute and chronic leukaemias, and clinically aggressive lymphomas (including Hodgkin's lymphoma) who were under treatment or within 12 months of achieving cure.
1.2	Consumers under follow up for chronic lymphoproliferative disorders including haemotological malignancies such as indolent lymphoma, chronic lymphoid leukaemia, myeloma, Waldenstrom's macroglobulinemia and other plasma cell dyscrasias. **Note** this list is not exhaustive but provides an indication of conditions where a consumer should receive a third primary dose.

2. Consumers on immunosuppressive or immunomodulating therapy at the time of vaccination

2.1	Those who were receiving or had received immunosuppressive therapy for a solid organ transplant in the previous six months.
2.2	Those who were receiving or had received in the previous three months targeted therapy for autoimmune disease, such as JAK inhibitors or biologic immune modulators including B-cell targeted therapies (including rituximab but in this case the recipient would be considered immunosuppressed for a six month period), T-cell co-stimulation modulators, monoclonal tumor necrosis factor inhibitors (TNFi), soluble TNF receptors, interleukin (IL)-6 receptor inhibitors, IL-17 inhibitors, IL 12/23 inhibitors, IL 23 inhibitors **Note** this list is not exhaustive but provides a guide on the types of scenarios where a consumer should receive a third primary dose.

CASE 2

Case Two

Haemoglobin	70	g/L	115-155
RBC	2.1	x10^12/L	3.6-5.6
HCT	0.23	L/L	0.35-0.46
MCV	111	fL	80-99
MCH	33.3	Pg	27-33
Platelet	173	x10^9	150-400
WBC	3.6	x10^9	4-11
Neutrophils	2.23	x10^9	1.9-7.5
Lymphocytes	0.94	x10^9	1-4
Monocytes	0.4	x10^9	0.2-1
Eosinophils	0.03	x10^9	<0.51
Basophils	0.02	x10^9	0-0.2

- Blood Film
  - Increased number of spherocyte and polychromatic cells seen

Differential diagnosis

1. B12 or folate deficiency
2. Liver disease
3. Medication related
   - EtOH
4. Hypothyroidism
5. Reticulocytosis
   - Blood loss
   - Haemolysis
6. Myelodysplastic syndrome
   - Sometime the peripheral blood dysplasia is not noticeable

Haemolysis 101

1. Increase haemoglobin breakdown
2. Evidence of compensatory erythroid hyperplasia
3. Evidence of red cell damage
4. Evidence of shorted red cell survival

1. Increase haemoglobin breakdown

- ↓Haptoglobin (sensitive)
  - Essentially exclude haemolysis if normal
  - Liver synthesis
- Urine haemosiderin (severity)
  - More likely in intravascular haemolysis
- ↑Bilirubin (unconjugated)
  - Often we just use total bili

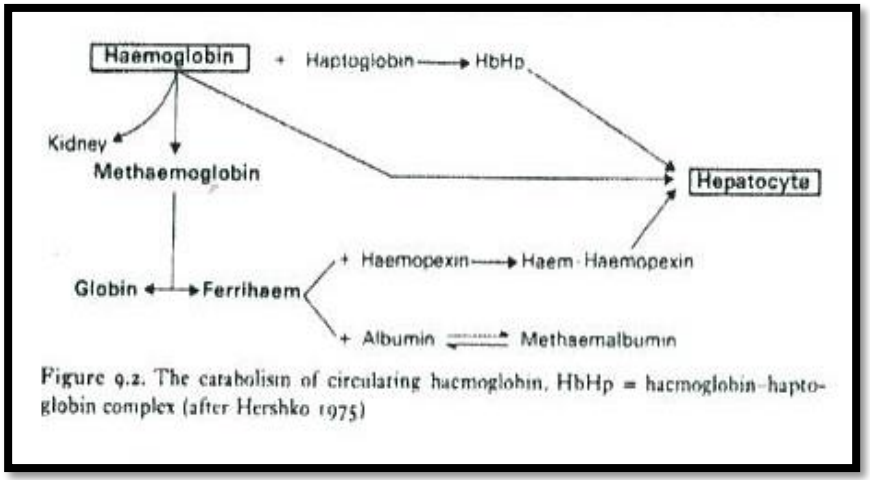


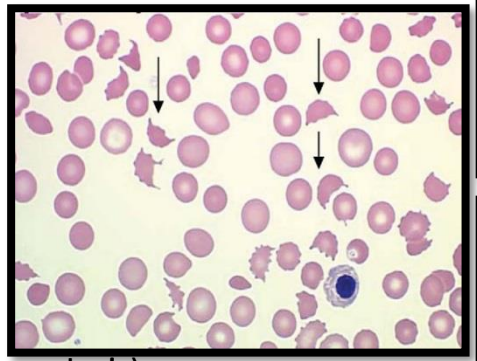
Figure 9.2. The catabolism of circulating haemoglobin. HbHp = haemoglobin–haptoglobin complex (after Hershko 1975)

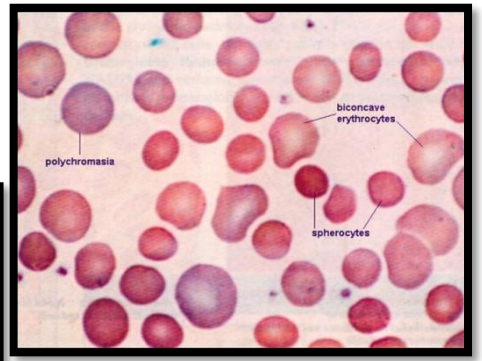
2. Evidence of compensatory erythroid hyperplasia

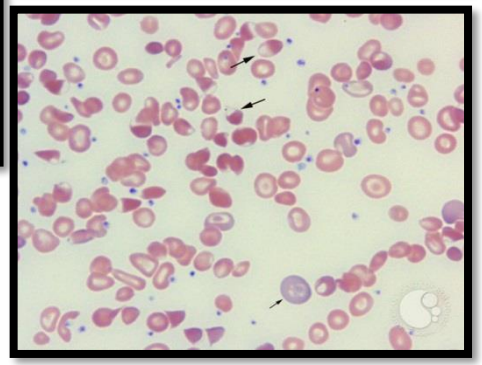
- Reticulocytosis
- ↑LDH

3. Evidence of red cell damage

- Morphological
  - Spherocyte
    - Immune mediated
    - Red cell membranopathy
  - Red cell fragments
    - Microangiopathic haemolysis
  - Blister cells
    - Metabolic (G6PD)
- Serological
  - Direct antiglobulin test (DAT/Coombe's)
    - IgG 1-2/4 (considered as normal)
    - C3D 1-2/4 (considered as normal)







4. Evidence of shorted red cell survival

- Anaemia
- Red cell survival study
  - ^{51}Chromium

So the story continue

	Feb 18	Mar 18	Nov 20	Feb 21	May 21
Haemoglobin	70	128	100	128	88
RBC	2.1	4.17	3.01	4.29	2.57
HCT	0.23	0.41	0.31	0.4	0.28
MCV	111	99	102	94	107
MCH	33.3	30.7	33.2	29.8	34.2
Platelet	173	266	285	349	351
WBC	3.6	8.0	4.0	14.8	6.0
Neutrophils	2.23	6.89	2.2	11.9	3.7
Lymphocytes	0.94	0.78	1.3	2.0	1.7
Monocytes	0.4	0.28	0.4	0.8	0.4
Eosinophils	0.03	<0.01	0,1	011	0.1
Basophils	0.02	0.01	<0.1	0.1	<0.1
Retic			163		229

https://www.ncbi.nlm.nih.gov › articles › PMC8200779

A Case of Autoimmune Hemolytic Anemia Following ...

by S Brito · 2021 · Cited by 2 — Keywords: **covid**-19 mrna **vaccine**, **autoimm**
anemia, sars-cov-2, warm **autoimmune hemolytic anemia**, immune-mediate
Abstract · Introduction · Case presentation · Discussion

https://journals.lww.com › hemasphere › Fulltext › Autoi...

Autoimmune Hematologic Disorders in Two Patients A

by ME Gaignard · 2021 — Autoimmune hematologic disorders such as immun
thrombocytopenia (ITP) or **autoimmune hemolytic anemia** (AIHA) have bee

https://onlinelibrary.wiley.com › doi › ijlh

A case of severe autoimmune hemolytic anemia after a

14/07/2021 — As **COVID**-19 large-scale **vaccination** efforts are underway an
vaccines have been delivered, reports about possible rare reactions or ...

https://www.mdpi.com › pdf PDF

SARS-CoV-2 and Autoimmune Cytopenia - MDPI

by R Quinn · 2021 — Keywords: autoimmune; cytopenia; **autoimmune hemo**
agglutinin syndrome; ... **COVID**-19 **Vaccination and Autoimmune** Cytopenia

https://pesquisa.bvsalud.org › covidwho-1278702

A Case of Autoimmune Hemolytic ... - Pesquisa .bvsalu

Autoimmune hemolytic anemia (AIHA) is a condition characterized by the in

https://www.ncbi.nlm.nih.gov › articles › PMC7267601

Autoimmune haemolytic anaemia associated with COVID-19 ...

by G Lazarian · Cited by 169 — The median time between the first **COVID**-19 symptoms and
AIHA onset was nine days (range 4–13 days), and haemoglobin level decreased by more than...

https://pubmed.ncbi.nlm.nih.gov › ...

COVID-19 associated with severe autoimmune hemolytic ...

by J Jacobs · 2021 · Cited by 18 — Background: **Autoimmune hemolytic anemia** (AIHA)
has many known disease associations, including autoimmune, lymphoproliferative, and...

https://casereports.bmj.com › content

Haemolytic anaemia: a consequence of COVID-19 - BMJ ...

by M Jawed · 2020 · Cited by 12 — This includes renal failure, thrombosis, cardiomyopathy and
the recently describe 'long **COVID**-19'.3–6 There have been a few cases reports of...

https://www.cureus.com › articles › 63138-a-case-of-co...

A Case of COVID-19-Associated Autoimmune Hemolytic ...

by Z Huda · 2021 · Cited by 1 — Information regarding **COVID**-19 and associated
coagulopathies is rapidly evolving and expanding. Thus far, many cases of **autoimmune**...

https://onlinelibrary.wiley.com › doi › trf

COVID-19 associated with severe autoimmune hemolytic ...

3/12/2020 — Abstract Background **Autoimmune hemolytic anemia** (AIHA) has many known
disease associations, including autoimmune, lymphoproliferative, ...

HEALTH

AstraZeneca COVID vaccine blood clot risk 'similar' to Pfizer, new study finds

OPEN

First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland

C. R. Simpson[1,2], T. Shi[2], E. Vasileiou[2], S. V. Katikireddi[3], S. Kerr[2], E. Moore[4], C. McCowan[5], U. Agrawal[5], S. A. Shah[2], L. D. Ritchie[6], J. Murray[4], J. Pan[7], D. T. Bradley[8,9], S. J. Stock[2], R. Wood[2,4], A. Chuter[10], J. Beggs[10], H. R. Stagg[2], M. Joy[11], R. S. M. Tsang[11], S. de Lusignan[11], R. Hobbs[11], R. A. Lyons[12], F. Torabi[12], S. Bedston[12], M. O'Leary[4], A. Akbari[12], J. McMenamin[4], C. Robertson[4,7] and A. Sheikh[2,10]

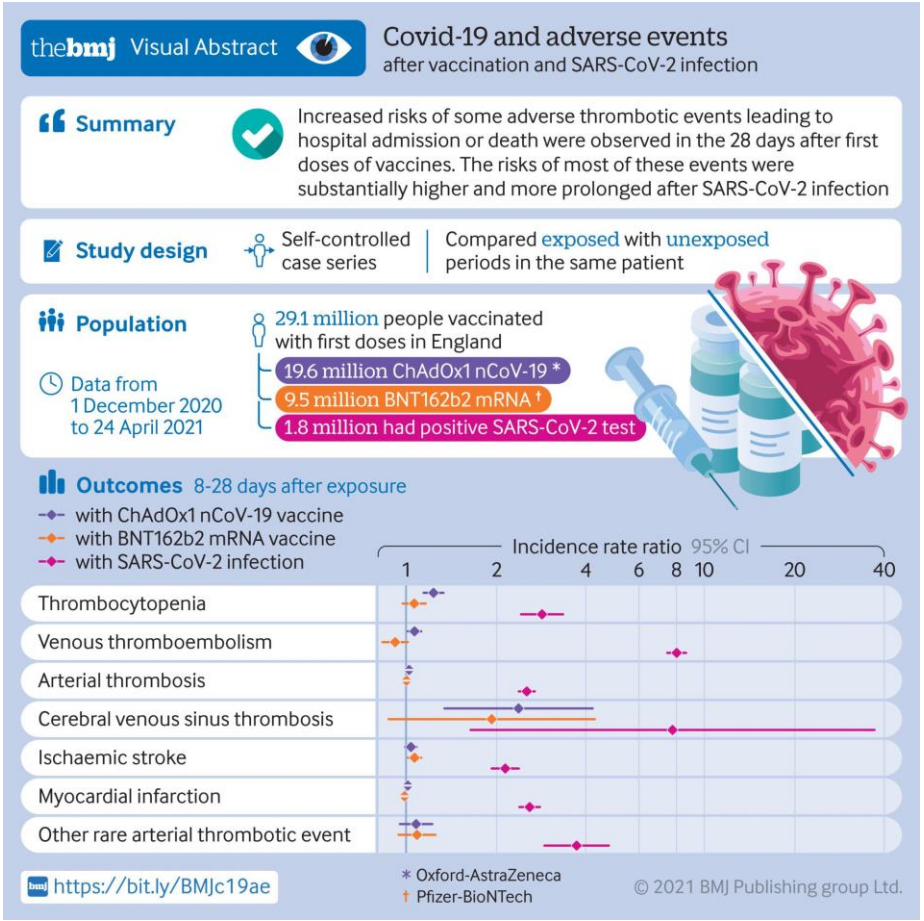
Nature Medicine. July 21

Reports of ChAdOx1 vaccine-associated thrombocytopenia and vascular adverse events have led to some countries restricting its use. Using a national prospective cohort, we estimated associations between exposure to first-dose ChAdOx1 or BNT162b2 vaccination and hematological and vascular adverse events using a nested incident-matched case-control study and a confirmatory self-controlled case series (SCCS) analysis. An association was found between ChAdOx1 vaccination and idiopathic thrombocytopenic purpura (ITP) (0–27 d after vaccination; adjusted rate ratio (aRR) = 5.77, 95% confidence interval (CI), 2.41–13.83), with an estimated incidence of 1.13 (0.62–1.63) cases per 100,000 doses. An SCCS analysis confirmed that this was unlikely due to bias (RR = 1.98 (1.29–3.02)). There was also an increased risk for arterial thromboembolic events (aRR = 1.22, 1.12–1.34) 0–27 d after vaccination, with an SCCS RR of 0.97 (0.93–1.02). For hemorrhagic events 0–27 d after vaccination, the aRR was 1.48 (1.12–1.96), with an SCCS RR of 0.95 (0.82–1.11). A first dose of ChAdOx1 was found to be associated with small increased risks of ITP, with suggestive evidence of an increased risk of arterial thromboembolic and hemorrhagic events. The attenuation of effect found in the SCCS analysis means that there is the potential for overestimation of the reported results, which might indicate the presence of some residual confounding or confounding by indication. Public health authorities should inform their jurisdictions of these relatively small increased risks associated with ChAdOx1. No positive associations were seen between BNT162b2 and thrombocytopenic, thromboembolic and hemorrhagic events.

Research

Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study

BMJ 2021 ; 374 doi: https://doi.org/10.1136/bmj.n1931 (Published 27 August 2021)
Cite this as: *BMJ* 2021;374:n1931



- Very confusing study
  - Their written conclusion is very different.
    - Probably too many subgroup analysis

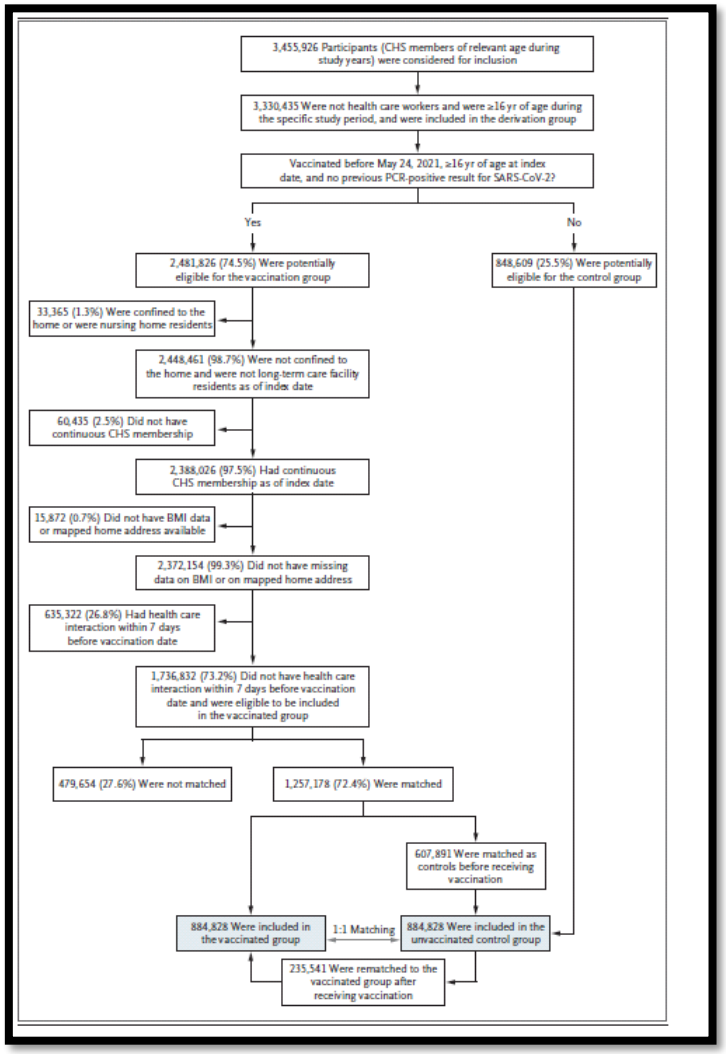
The NEW ENGLAND JOURNAL of MEDICINE

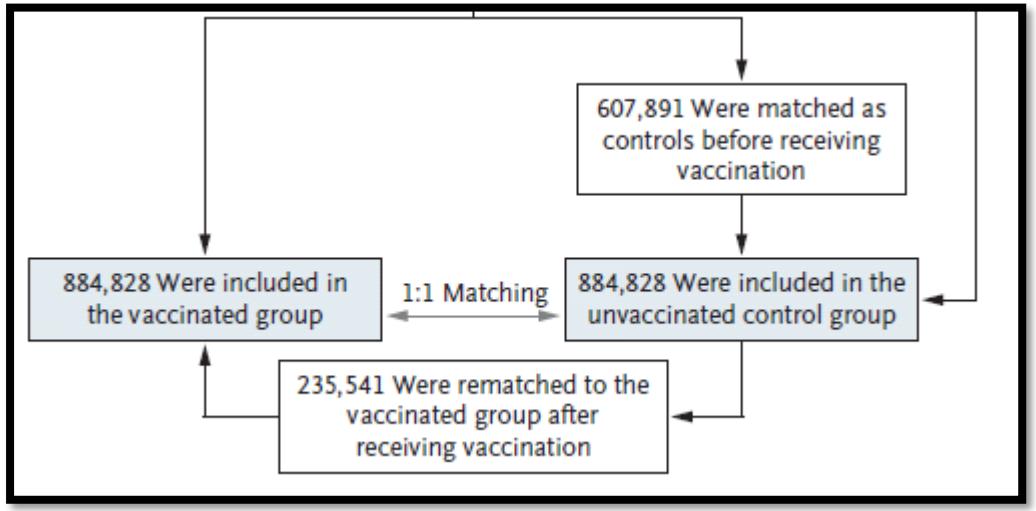
ORIGINAL ARTICLE

Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting

Noam Barda, M.D., Noa Dagan, M.D., Yatir Ben-Shlomo, B.Sc., Eldad Kepten, Ph.D., Jacob Waxman, M.D., Reut Ohana, M.Sc., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Isaac Kohane, M.D., Doron Netzer, M.D., Ben Y. Reis, Ph.D., and Ran D. Balicer, M.D.

NEJM. Sep 21


3,455,926 Participants (CHS members of relevant age during study years) were considered for inclusion
3,330,435 Were not health care workers and were ≥16 yr of age during the specific study period, and were included in the derivation group
Vaccinated before May 24, 2021, ≥16 yr of age at index date, and no previous PCR-positive result for SARS-CoV-2?
Yes
No
2,481,826 (74.5%) Were potentially eligible for the vaccination group
848,609 (25.5%) Were potentially eligible for the control group
33,365 (1.3%) Were confined to the home or were nursing home residents
2,448,461 (98.7%) Were not confined to the home and were not long-term care facility residents as of index date
60,435 (2.5%) Did not have continuous CHS membership
2,388,026 (97.5%) Had continuous CHS membership as of index date
15,872 (0.7%) Did not have BMI data or mapped home address available
2,372,154 (99.3%) Did not have missing data on BMI or on mapped home address
635,322 (26.8%) Had health care interaction within 7 days before vaccination date
1,736,832 (73.2%) Did not have health care interaction within 7 days before vaccination date and were eligible to be included in the vaccinated group
479,654 (27.6%) Were not matched
1,257,178 (72.4%) Were matched
607,891 Were matched as controls before receiving vaccination
884,828 Were included in the vaccinated group
1:1 Matching
884,828 Were included in the unvaccinated control group
235,541 Were rematched to the vaccinated group after receiving vaccination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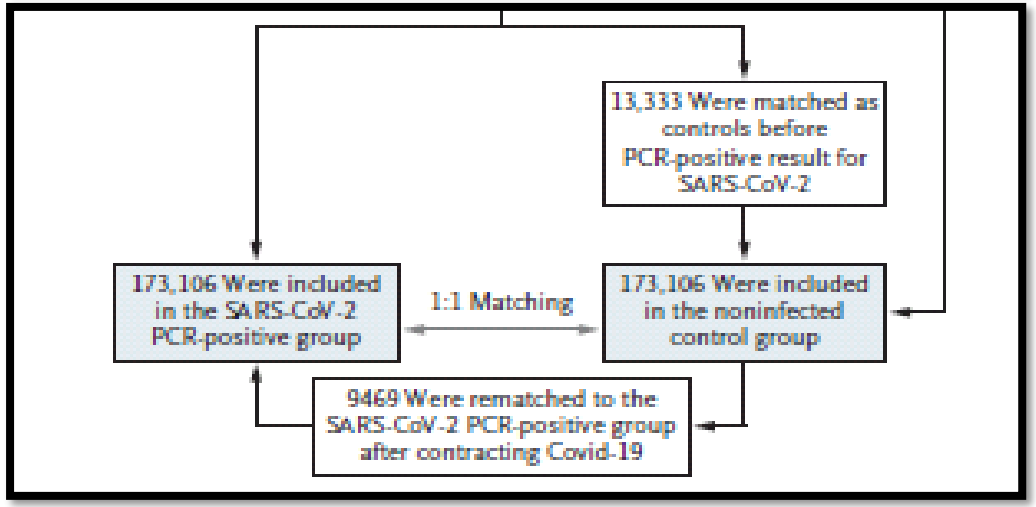
13,333 Were matched as controls before PCR-positive result for SARS-CoV-2
173,106 Were included in the SARS-CoV-2 PCR-positive group
1:1 Matching
173,106 Were included in the noninfected control group
9469 Were rematched to the SARS-CoV-2 PCR-positive group after contracting Covid-19

Table 2. Adverse Events Associated with SARS-CoV-2 Vaccination.*

Event	Adverse-Event Cohort in Each Group	Vaccinated Group	Control Group	Risk Ratio (95% CI)	Risk Difference (95% CI)
	no. of persons	*no. of events*			*no. of events/100,000 persons*
Acute kidney injury	912,019	20	45	0.44 (0.23 to 0.73)	−4.6 (−7.8 to −1.8)
Anemia	709,267	298	378	0.79 (0.67 to 0.93)	−18.7 (−32.1 to −6.1)
Appendicitis	900,289	95	66	1.40 (1.02 to 2.01)	5.0 (0.3 to 9.9)
Arrhythmia	856,152	254	284	0.89 (0.74 to 1.04)	−6.1 (−14.7 to 1.8)
Arthritis or arthropathy	731,340	64	70	0.95 (0.65 to 1.34)	−0.8 (−6.3 to 4.2)
Bell's palsy	923,692	81	59	1.32 (0.92 to 1.86)	3.5 (−1.1 to 7.8)
Cerebrovascular accident	917,598	45	55	0.84 (0.54 to 1.27)	−1.6 (−5.3 to 2.0)
Deep-vein thrombosis	925,380	39	47	0.87 (0.55 to 1.40)	−1.1 (−4.5 to 2.7)
Herpes simplex infection	876,328	219	205	1.13 (0.95 to 1.38)	4.8 (−1.9 to 12.4)
Herpes zoster infection	888,647	283	204	1.43 (1.20 to 1.73)	15.8 (8.2 to 24.2)
Intracranial hemorrhage	933,130	13	30	0.48 (0.20 to 0.89)	−2.9 (−5.6 to −0.5)
Lymphadenopathy	823,006	660	279	2.43 (2.05 to 2.78)	78.4 (64.1 to 89.3)
Lymphopenia	938,939	2	7	0.26 (0.00 to 1.03)	−0.9 (−2.0 to <0.1)
Myocardial infarction	892,785	59	60	1.07 (0.74 to 1.60)	0.8 (−3.3 to 5.2)
Myocarditis	938,812	21	6	3.24 (1.55 to 12.44)	2.7 (1.0 to 4.6)
Neutropenia	919,291	20	22	0.87 (0.46 to 1.66)	−0.5 (−2.8 to 1.8)
Other thrombosis†	932,469	12	22	0.46 (0.19 to 0.91)	−2.2 (−4.6 to −0.3)
Paresthesia	827,478	552	496	1.12 (0.98 to 1.24)	10.8 (−1.8 to 21.4)
Pericarditis	936,197	27	18	1.27 (0.68 to 2.31)	1.0 (−1.6 to 3.4)
Pulmonary embolism	937,116	10	17	0.56 (0.21 to 1.15)	−1.5 (−3.6 to 0.4)
Seizure	913,091	36	35	0.99 (0.62 to 1.64)	−0.4 (−3.0 to 3.1)
Syncope	858,068	326	267	1.12 (0.94 to 1.34)	6.2 (−3.2 to 15.4)
Thrombocytopenia	923,123	56	60	0.94 (0.63 to 1.27)	−0.6 (−4.6 to 2.3)
Uveitis	933,217	26	20	1.27 (0.68 to 2.67)	1.0 (−1.5 to 3.8)
Vertigo	773,263	433	395	1.12 (0.97 to 1.28)	9.3 (−2.5 to 20.0)

* Estimates were calculated with the use of the Kaplan–Meier estimator 42 days after vaccination or SARS-CoV-2 infection. Confidence intervals (CIs) were estimated with the use of the percentile bootstrap method with 500 repetitions.
† The "other thrombosis" category is a composite diagnosis that includes arterial embolism and thrombosis, venous embolism and thrombosis, vascular insufficiency of the intestine, portal-vein thrombosis, or cranial venous sinus thrombosis.

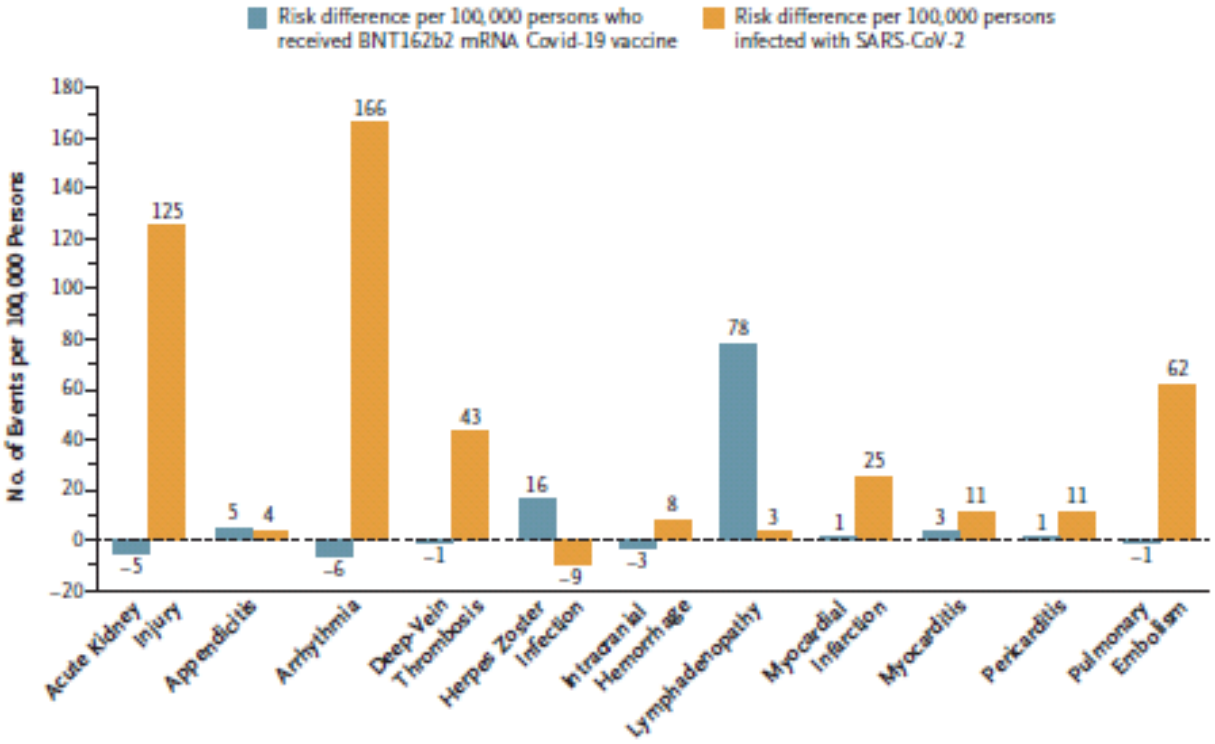

Figure 4. Absolute Excess Risk of Various Adverse Events after Vaccination or SARS-CoV-2 Infection.

Point estimates of the risk differences for selected adverse events are shown. Estimates were derived 42 days after vaccination or SARS-CoV-2 infection with the use of the Kaplan–Meier estimator. Risk differences are shown per 100,000 persons and rounded to the nearest integer. Negative differences (decreased risk) are represented as negative values on the y axis, and positive differences (increased risk) are represented as positive values on the y axis. The abbreviation mRNA denotes messenger RNA.