bijwerkingen centrumlareb

Overview of reports with fatal outcome after COVID-19 vaccination in the first 14 weeks of the Dutch vaccination campaign.

1. Introduction

The Dutch COVID-19 vaccination campaign started on January 6th, 2021. The first vaccines went to corona-ward-related hospital- and ambulance staff, who were vaccinated on location in their hospitals, as well as nursing home staff at municipal health authority (GGD) locations. On January 18th, 2021 the first nursing home resident was vaccinated, kicking off a large scale vaccination of long-term residential care facilities. As of January vaccination of mobile, independently living elderly began, starting with the 90+ generation and adding younger age groups in 5-years brackets, the latest addition being the 70-74 year old's, as of April 6th.

This is the second overview of reports with a fatal outcome received by Lareb. The first one on 94 cases, cutoff date February 26th, covering the first 8 weeks of the Dutch COVID-19 vaccination campaign was published in March, 2021. The current overview reviews the 264 cases received until April 15th, 2021. The previously reported cases are included in this new overview.

The goal of this overview is to give insights into:

1. background and description of the cases
2. patterns of adverse events and their relationship with fatal outcome
3. potential contribution of the reported adverse reactions to the fatal outcome

This is report is a descriptive overview, it does not include analyses of signals for specific adverse events. In case of an indication to do so, these analyses are performed separately. Cases in this report that mention specific adverse events are also taken into account in these separate analyses.

2. Vaccination strategy

Since the start of the vaccination campaign, the Dutch National Institute for Public Health and the Environment (RIVM) publishes weekly cumulative reports on vaccination metrics. Pfizer's Comirnaty was the first vaccine to be approved in and delivered to the Netherlands. Therefore the vast majority of the elderly population received this vaccine. (Table 1) Astra Zeneca vaccines, for which the time between first and second dose is substantially longer than for the Moderna and Pfizer vaccines, were just starting to be given for the second time around the cutoff date for this overview. All 264 individuals in this overview were vaccinated on or prior to April 14th.

Table 1: Vaccination figures January 6th to April 13th 2021

Target group	Start date	Vaccine	First dose	Second dose	Total
Living at home, vaccinated by GGD:					
90-plus	26-01-2021	PFIZ	64.485	56.779	121.264
85-89 year old	29-01-2021	PFIZ	179.811	156.183	335.994

Target group	Start date	Vaccine	First dose	Second dose	Total
80-84 year old	05-02-2021	PFIZ	352.780	241.517	594.297
75-79 year old	06-03-2021	PFIZ	338.048	17.119	355.167
70-74 year old	06-04-2021	PFIZ	158.008	2.105	160.113
Others vaccinated by GGD	06-01-2021	PFIZ/AZ	428.161	205.494	633.655
Those vaccinated by general practitioners (estimated)	15-02-2021	AZ	707.989	0	707.989
Those vaccinated by other health care providers (estimated)	06-01-2021	PFIZ/MOD /AZ	728.495	146.938	875.433
Total			2.957.777	826.135	3.783.912

PFIZ= Comirnaty® (BioNTech/Pfizer); MOD=COVID19 Vaccine Moderna®, AZ= Vaxzevria® (Astra Zeneca)

https://www.rivm.nl/sites/default/files/2021-04/Wekelijkse%20rapportage%20COVID-19%20Vaccinatiegraad_13_04_2021_versie%202.pdf

3.Reports

Lareb received 264 reports in which a fatal outcome was reported in the first 14 weeks of the Dutch COVID-19 vaccination campaign, with cutoff date of April 15, 2021, end of day. Excluded from this analysis are 7 reports, which only contained the information that a person had died after vaccination, without further details. All 7 reports came from consumers, including 1 reported to Pfizer, the marketing authorization holder (MAH) of one of the vaccines. Some serious cases reported prior to April 15 had evolved to a fatal outcome when the reporter was contacted again for additional information (follow up). In case the date of death was after April 15, these cases were not taken into account in the present overview.

After receipt of reports, with the exception of those received indirectly through the MAH, Lareb evaluates the information received. If more information is needed , which is the case in the large majority of the reports, Lareb contacts the reporter and asks for follow-up information. If not received within a few weeks, Lareb sends out reminder e-mails, or contacts the reporter by phone. When this overview was written, not all follow up had yet been obtained for all reports.

Table 2. Reports received

Spontaneous reports received	264
Lareb Intensive Monitoring (LIM)	0
Reports excluded due to minimal information*	-7
Total included in this overview	257

*reports only mentioned that a person had died after vaccination, without any further detail.

Figure 1 Vaccines administered in the reports we received

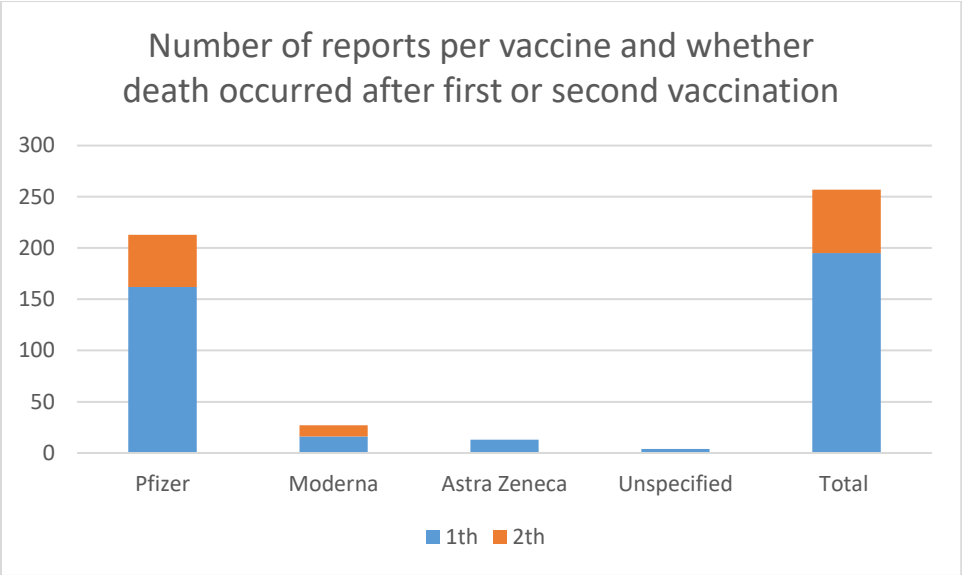

Table 3 Vaccines administered in the reports we received

Vaccine	After 1 vaccination	After 2 vaccinations	Total	
Pfizer	162	51	213	83%
Moderna	16	11	27	11%
Astra Zeneca	13	0	13	5%
Unspecified	4	0	4	2%
Total	195	62	257	100%

Table 4 Reporters

Reporter	
General Practitioner	**82**
Consumer	**60**
Elderly care physician	**37**
Medical specialist excl. Elderly care physicians	**36**
Other physician	**25**
Nurse, nurse practitioner, physician assistant	**3**
Nurse assistant (‘ziekenverzorgende”)	**1**
Other (e.g. medical students, interns)	**12**
Total	**257**

Lareb’s reporting forms do not ask for a specification whether the deceased was living independently or in a long term care facility, so we cannot identify them for separate analysis. For reports from elderly care physicians it can be assumed with a high level of confidence that the person reported on was a nursing home resident. Health care in the Netherlands, however, is organized in such a way,

that also general practitioners take part in the care of long term care residents. So also their reports include long term care residents, as well as the reports from other sources.

The group "Other physicians" generally includes junior physicians in training in either the long term care facilities, the GP practices or hospitals. Some reports are done by medical examiners, called in to officially establish death, which is routine practice for deaths outside of hospital. The medical examiner can be the patient's own general practitioner, a colleague general practitioner on call that evening/weekend or a GGD (Gemeentelijke Gezondheidsdienst= municipal health authority) forensic medicine specialist. The latter is consulted in case the general practitioner does not feel able to declare a death of natural causes, which is sometimes the case when there were no witnesses to the death.

Table 5 Gender and age

age/gender	male	female	total	%
<65	4	9	13	5%
65-79	25	18	43	20%
80-89	64	64	128	48%
90+	24	48	72	25%
unknown		1	1	0%
total	117	140	257	100%
%	46%	54%		

3.1 Fragility

In research in elderly people the clinical frailty index, scoring people from 1 (very fit) to 9 (terminally ill), is a useful tool. Unfortunately we do not have enough details about the deceased in this overview to be able to apply this tool. In addition, not all people in our overview were elderly. In various reports the deceased were described by the reporters as being in a very fragile an vulnerable stage of their lives. In other reports remarks were made about the relatively healthy states of the deceased. In order to capture such information we have introduced a label, which we called "fragility", which should not be understood as an official validated method and is somewhat arbitrary. We labelled the cases according to the following categories:

- Fragile: the deceased was described as "very fragile nursing home resident" and/or in end stages of a fatal disease, such as end stage metastasized cancer, and/or patients with serious and potentially fatal underlying illness, such as heart failure or end stage renal disease or COVID19 that already existed prior to vaccination and/or patients with at least 5 relevant comorbidities.
- Somewhat fragile: cases in which the deceased did not classify for the above but were 90+ years old and/or living in a nursing home due to advanced dementia and/or had underlying disease that already caused events, such as TIA's, CVA's, myocardial infarctions in the past and/or had at least 3 cardiovascular medications and/or were on a clear downward slope (e.g. progressive dyspnea) in the months/weeks prior to vaccination.
- Hardly fragile: not classifying for the above and ≥ 70 years old without reported underlying disease or < 70 year with well controlled underlying disease without recent events.
- Not fragile: < 70 years old and no relevant underlying disease or condition reported

Table 6 Fragility

Fragility		
Fragile	**93**	**36%**
Somewhat fragile	**97**	**38%**
Hardly fragile	**16**	**6%**
No fragility	**0**	**0%**
Not (yet) assessable	**51**	**20%**
Total	**257**	**100%**

3.2 Comorbidities

Whether the deceased had suffered from a COVID-19 infection in the past is a standard question on our reporting forms. In 232/257 this question was answered. In 32/232 (=14%) the answer was positive.

Table 7 Prior COVID-19 infection

(Suspected) COVID-19 in the past		
Yes	**32**	**12%**
No	**200**	**78%**
Unknown	**25**	**10%**
Total	**257**	**100%**

Table 8 lists medical history, where known, following the MedDRA SOC classification. There is a subset of cases where no or incomplete follow up information has been received. In addition, some consumers report not to be fully aware of the medical history of the deceased and there are cases where the reporting physician does not have full access to or knowledge of the patient history, e.g. when the reporter is the medical examiner or when the deceased had a severe care avoiding nature.

A total of 179 nervous system disorders were reported in 122 people. The most reported single underlying comorbidity was dementia, in various types and levels of severity, which was reported in 29% of all reports of this overview. CVA and TIAs were reported 48 times in patient's medical history.

In 96 cases a total of 151 cases of cardiac disorders were reported. The underneath table lists them separately, off note however, 66/96 people had either cardiac failure or atrial fibrillation or both. In addition to these 96 reports, another 7 reported procedures or test results indicating cardiac disease, without mentioning a cardiac medical history, such as the presence of murmurs, abnormal findings on the ECG, stent placement, cardiac artery bypass, cardiac valve prosthesis, the presence of pacemaker or other "cardiac devices".

Fifty nine times the medical history reported "hypertension" or "hypertensive crisis", in twenty nine of these cases no cardiac history was reported. In 9 of them cerebrovascular events were reported. Twenty reports of hypertension did not report either cardiac or cerebrovascular disease or procedures in the medical history.

In 154/257 cases a vascular and/or a cardiac and/or a cerebrovascular condition or event was mentioned in the medical history, pointing towards the presence of cardiovascular risk. Diabetes mellitus, another cardiovascular risk factor, was present in several of these cases. In addition, there were 12 cases with diabetes mellitus without the aforementioned events or conditions in their

history bringing it to 166/257. This leaves only 91 cases in which such history was not mentioned, or no medical history was available at all. For lack of precise data other risk factors such as smoking behavior were not included (separate analysis, not visible in below table) .

Table 8 Medical history/comorbidity -details

SOC	**Number of reported conditions (nr. of patients)**	**Most frequently reported conditions (not mutually exclusive)**	Total
Nervous system disorders	**179 (122)**	Dementia (including mixed, vascular and Alzheimer) (n=59) Cognitive Disorder, memory impairment (n=9) Intellectual Disability (n=6)	74
		Cerebrovascular Accident (n=17) (Ischemic) Cerebral Infarction, incl. ischemic stroke, lacunar infarction, thalamic infarction (n=14) Cerebral Arteriosclerosis (n=1) Cerebral Hemorrhage (n=0) Transient Ischemic Attack (n=16) *Syncope *(n=2)* *Monoparesis/plegia, Hemiparesis/plegia*, Paresis, Dysarthria* (n=7)* *Aphasia, Depressed consciousness* (n=2)*	48 (*59*)
		(Vascular) Parkinson(ism)	15
		Epilepsy, Seizure, Post Ictal State	10
		(Poly)neuropathy: peripheral, axonal, diabetic, small fiber	7
		(Leuko)encephalopathy, Multiple Sclerosis, Multiple System Atrophy	4
		(Ophthalmic) Migraine and headache	4
		Others (each n=1 or 2)	6
Cardiac disorders	**151 (96)**	Cardiac Failure (n=43) Cardiac Asthma (n=3) LV dysfunction (n=2)	48
		Atrial Fibrillation (n=35) Atrial Flutter (n=1) Supraventricular extrasystole (n=2) Sinus node dysfunction (n=1)	39
		AV Block (n=1) BBB (n=1) Ventricular Extrasystoles (n=2) Ventricular Tachycardia (n=1) Ventricular Fibrillation (n=1)	6
		Arrhythmia (n=6)	9

		Palpitations (n=3)	
		Myocardial Infarction (n=13) Angina Pectoris (n=7) Coronary Artery Disease (n=4) Myocardial Ischemia (n=4) Acute Coronary Syndrome (n=1)	29
		Aortic Valve Stenosis (n=8) Mitral Valve Stenosis (n=2) Mitral Valve Insufficiency (n=3) Heart Valve Insufficiency (n=1)	14
		Cardiac Disorder (n=3) Cardiomyopathy (n=2) Cardiac Arrest (n=1)	6
Vascular disorders	**88(77)**	Hypertension (n=58) Hypertensive Crisis (n=1)	59
		Aortic Aneurysm (n=4) Aortic Disorder (n=1)	5
		Peripheral Vascular Disorder (n=4) Deep Vein Thrombosis (n=4) Peripheral Venous Disease (n=2) Claudication Intermittent (n=3) Peripheral Arterial Occlusive Disease (n=2) Peripheral Artery Aneurysm (n=1)	16
		Thrombosis (n=2) Arteriosclerosis (n=2) Angiopathy (n=1) Aneurysm (n=1) Infarction (n=1) Circulatory Collapse (n=1)	8
Endocrinology			
	63(60)	Diabetes Mellitus (n= 34) Type 2 Diabetes (n=15) Impaired glucose tolerance/Blood glucose abnormal (n=2) Type 1 Diabetes (n=1)	52
		Hypothyroidism (n=5) Hyperthyroidism (n=3) Other Thyroid (n= 2)	10
		Other	1
Infections and Infestations	**70(63)**	(Suspected) COVID	32
		Urinary Tract Infection (n=10) Cystitis (n=3) Urosepsis (n=1)	14
		Pneumonia (n=7) Respiratory Tract Infection (n=3) Bronchitis (n=2)	13

		Nasopharyngitis (n=1)	
		Erysipelas (n=2) Cellulitis (n=1)	3
		Other (each n=1)	8
Respiratory disorders	**50(42)**	Chronic Obstructive Pulmonary Disease (n=22) Asthma (n=4)	26
		(Exertional) Dyspnea and orthopnea	7
		Bronchiectasis/pathy, Emphysema, Pulmonary Hypertension, Pulmonary Embolism	6
		Bronchitis, Cough, Aspiration Pneumonia	5
		Unspecified lung disorder, Respiratory disorder, Respiratory failure	4
		Other (each n=1)	2
Neoplasms	**48(39)**	Basal Cell Carcinoma (n=8) Squamous Cell, Malignant Melanoma, undefined skin cancer (n=4)	12
		Prostate cancer (n=7) Benign Prostate Hyperplasia	8
		Myelodysplastic Syndrome (n=3) Plasma Cell Myeloma (n=2) Non-Hodgkin lymphoma, Leukemia	7
		Breast cancer (n=5) Benign Breast Hyperplasia	6
		Colon cancer	5
		Pancreas cancer	2
		Other (each n=1)	8
Renal Disorders	**46(39)**	Renal impairment (n=15) Renal failure (n=14) Chronic Kidney Failure (n=2) Diabetic Nephropathy (n=1)	32
		Urinary Incontinence ,Micturition Disorder	4
		Calculus Urinary, Nephrolithiasis	3
		Urinary Retention (n=2) Other (n=5, each n=1)	7
Gastro Intestinal Disorders	**30(28)**	Gastroesophageal Reflux Disease (n=4) Diaphragmatic Hernia/ Hiatus Hernia (n=4)	8
		Constipation, Diarrhea, Defecation disorder	4
		Colitis, Hemorrhagic erosive gastritis	3
		Dysphagia	3
		Gastric Haemorrhage, Rectal Haemorrhage	2
		Inguinal Hernia	2
		Other (each n=1)	8
Psychiatric Disorders	**24(20)**	Delirium, Agitation, Confusional state	6

		Depression/Depressed mood	6
		Psychotic/Schizophrenic	3
		Other (each n=1 or 2)	9
Hematology	**19(25)**	Anemia (including normocytic, microcytic, iron deficiency, Coombs+hemolytic)	19
		Waldenstrom's macroglobulinemia, hypergammaglobulinemia, splenectomy, monoclonal B cell lymphocytosis	5
		Factor V Leiden, thrombopenia, immune thrombocytopenia, (thrombocytopenic) purpura	5
Immune System Disorders	**3(3)**	Sarcoidosis (n=2) Other (n=1)	3

**events in italics are not MedDRA HLGT Central nervous system vascular disorders, but other HLGT within SOC Nervous System Disorders, they are grouped here because they may represent symptoms of central nervous system vascular disorders*

In addition to the above, there was a large category of "other" including various eye disorders cataract, macular edema, glaucoma; disabilities such as blindness, deafness, bedridden, wheelchair use; muscle skeletal disorders such as arthritis, osteoarthritis, gout, rheumatoid arthritis, arthrodesis and various fractures; some vitamin deficiencies and electrolyte balance disturbances, weight increases, decreases and obesity; GI procedures such as appendectomy, gastric bypass, stoma, hemodialysis. None appeared in such numbers that they appeared relevant for this overview.

**events in italics are not MedDRA HLGT Central nervous system vascular disorders, but other HLGT within SOC Nervous System Disorders, they are grouped here because they may represent symptoms of central nervous system vascular disorders>*

3.3 Comedication

Whether and which medication was used was reported in the majority of cases. In 51/257 cases no medication was (yet) reported. Table 9 lists the medication that has been reported.

Table 9 Comedication

Category (ATC code)	**Number (patients)**	**Most frequently reported (not mutually exclusive)**	
Cardiovascular (C)	**353(119)**	Diuretics	78
		Beta blockers	66
		Statins and other lipid lowering	63
		ACE inhibitors	48
		Calcium Antagonists	41
		Angiotensin Receptor Blockers	28
		Vasodilators	13
		Glycosides	8

		Anti-arrhythmic	5
		Others	3
Antithrombotic agents (B01)	**106(102)**	Platelet aggregation inhibitors	54
		Vitamin K Antagonists	28
		DOAC's	22
		Heparins	2
Nervous system (N03-07))	**78(122)**	Anxiolytics	32
		Antipsychotics	27
		Antidepressants	24
		Anti-epileptics	18
		Anti-Parkinson	14
		Hypnotics	9
		Other	5
Analgesics (N02)	**71 (58)**	Paracetamol	41
		Fentanyl	15
		Oxycodon	6
		Morphine	4
		Tramadol/Paracetamol	4
		Other	2
Respiratory drugs (R)	**65(30)**	Salbutamol, Salmeterol and similar	25
		Fluticasone, Beclomethasone, Budesonide	17
		Ipratropium, Tiotropium and similar	13
		Antihistaminic	4
		Mucolytic	4
		Other	2
Drugs is diabetes (A10)	**64(46)**	Metformine	31
		Sulfonylureas	13
		Insulins	18
		Other	2
Antibiotics and Antimycotics (J)	**19(18)**	Amoxicillin	4
		Azithromycin	4
		Nitrofurantoin	4
		Others	7
Corticosteroids	**12(12)**	Prednisone or Prednisolone	9
		Dexamethasone	3

In addition to the above 160 patients took other medications, including many vitamins, e.g. at least 75 people took colecalciferol or other Vit D medication. Proton pump inhibitors, especially omeprazole and pantoprazol were used by at least 79 people and Macrogol by at least 37.

3.4 Co-suspects

In 20/257 cases the reporters have named comedication as “co-suspect” for potential roles in the events leading to death. In 16 cases 1 co-suspect was mentioned, in 4 cases 2 co-suspects were mentioned so total was 24 co-suspect drugs.

Table 10 Co-suspect medication

ATC-Code	Medication	Nr of times mentioned as co-suspect
B01A Vitamin K antagonists	Acenocoumarol	7
	Rivaroxaban (n=2), Apixaban (n=1) , Clopidogrel (n=1)	4
N02A/B Opioids/Other analgesics	Morphine, Fentanyl patch, Oxycodon, Paracetamol (n=1 for each)	4
C03/ C08 Diuretics/Calcium channel blockers	Bumetanide (n=2), Verapamil	3
H02/L04 Corticosteroids/immune suppressants	Prednisone, Tacrolimus, Methotrexate (n=1 for each)	3
Other	Clozapine, Ethinylestradiol/Levonorgestrel, Goserline (n=1 for each)	3
	Total	24

In the 7 reports in which acenocoumarol was reported as co-suspect, 2 suffered from ischemic events, 2 from hemorrhagic events, in the other 3 cases this is not clear. In addition to these, 22 further reports in the dataset describe use of Acenocoumarol, 13 of these were reported as cardiac deaths, 3 were pneumonia’s, of which 1 COVID-19 related, 1 CVA and 1 pulmonary embolism, in the remaining 4 cases cause of death was unknown.

4.Reported reactions and events

In 124/257 reports adverse events of reactogenicity, as listed below, were reported. In the remaining 133 reports, such events were not (yet) mentioned. At the time of this overview not all follow up on all reports had been obtained. But even if follow up is obtained, it is not always known or clear whether such adverse events occurred. Sometimes the reporter had not spoken to the deceased in the days between vaccination and death, in some cases people suffered from dementia and could not express their side effects and in other cases the reporter had not heard the deceased complain about side effects, but could not say for certain they had not occurred. Only in a small minority of these cases the reporter could ascertain no such events had occurred.

It should be noted that some of these adverse events occurred >7 days after the vaccination and may not always have been related to reactogenicity. In addition, some reporters noted that the strain on some of the elderly to travel to the vaccination locations, walk substantial distances from the car park, wait in line etc. may have elicited events in some cases, independent of the vaccine itself.

Table 11. Reactions reported after vaccination

Reactions reported (not mutually exclusive):	**Nr of people experiencing at least one of these events**	**Nr of events**
Any of the below	124	286
Malaise (n= 73) Nausea (n= 32) Vomiting (n=13)	86	118
Hyperpyrexia* (n=4) Pyrexia (n=40) Body temperature increased (n=6) Chills (n=18)	58	68
Fatigue (n=46) Arthralgia (n=12) Headache (n=12) Myalgia (n=17)	60	87
Injection site pain (n=7) Injection site erythema (n=2) Injection site inflammation/warmth (n=3) Injection site swelling (n=1)	9	13
**hyperpyrexia = >40.5 Celsius* *Please note: The same patient can have events out of various groups, so the nr. of patients do not add up to the total of 124. The number of events does add up.*		

4.1 Latency

In all reported cases, the vaccination date is known. In 224/257 reported cases, an exact day of death and hence an exact latency period between vaccination and death can be calculated. In the remaining 33 cases a 'maximum latency' can be calculated from the difference between vaccination date and reporting date. The longest latency in this data set is 61 days, which is based on an estimate of day of death. The longest latency in the 224 reports with exact knowledge is 34 days.

Figure 2 Latency between day of last vaccination and death

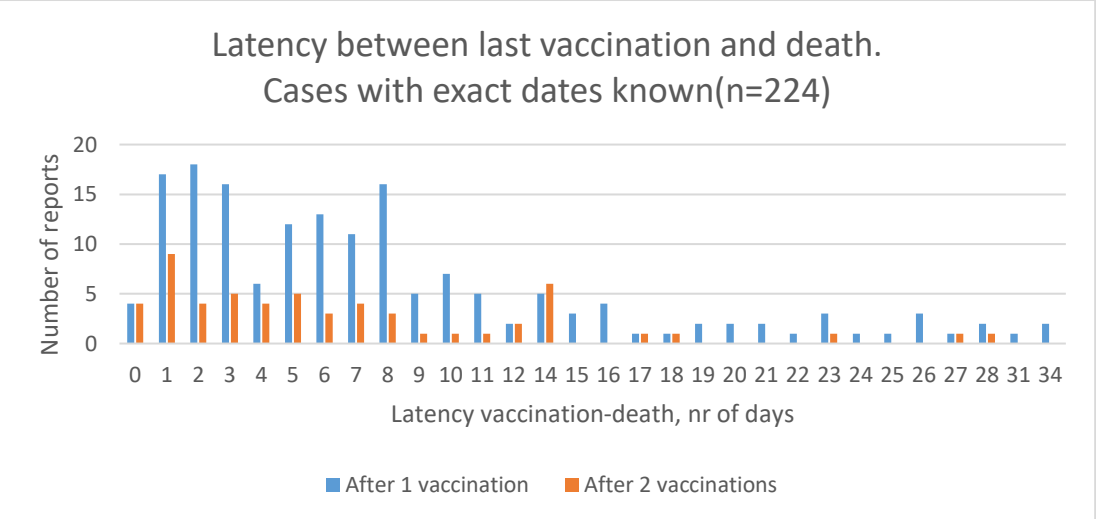

Table 12 Latency between day of last vaccination and death

Latency (days)	Number of reports (%)	Reports with death reported after 1 vaccination (%)	Reports with death reported after 2 vaccinations (%)
0-1	34 (15%)	21 (13%)	13 (23%)
2-7	101 (45%)	76 (45%)	25 (44%)
8-14	54 (24%)	40 (24%)	14 (24%)
>14	35 (16%)	30 (18%)	5 (9%)
Total	224 (100%)	167 (100%)	57 (100%)

4.2 Reported causes of death

Reported causes of death are listed in table 13. These are the causes reported to Lareb and do not necessarily correspond to the causes filled out on death certificates, as reporting consumers are rarely aware of what was filled out on the forms.

In 73 cases, the primary cause is currently “unspecified”. In some of these cases follow up information has been asked for, but has not yet been received. In some cases the physicians who reported the death were not in a position to provide any details, e.g. because they only saw the patient in their capacity of medical examiner to legally certify the death, or because they were emergency unit physicians without access to further details. In others, the deceased were found death, without a clear picture of what happened in the hours or even days prior to the death, so these will remain unspecified.

In eleven cases obduction has been done. In 3 cases we have not yet received results, in 3 cases macroscopy did not point into any direction, microscopy is awaited, in 3 cases myocardial infarctions based on (very) severe atherosclerosis could be established and 2 had other causes, including 1 pulmonary embolism.

In 63 of the cases the fatal outcome occurred after the second vaccination. These cases were not majorly different from the overall cases. In 24 cases the cause of death was not (yet) known, in 20 cases there was a cardiac cause, 3 times “dyspnea” or oxygen saturation decrease were given as cause of death, 3 pneumoniae, 1 pulmonary embolism, 2 respiratory failures in 2 cases a cerebrovascular accident. The remaining 8 cases included 1 death of COVID-19 very shortly after 2nd vaccination and 1 case of no cause was identified.

Table 13 Reported primary causes of death

Unspecified:		Reports that describe that the cause of death is and will remain unknown	24
		Reports in which a specification of the cause of death has not yet been received	38
		Sudden Death (so in very short time frame), without known cause	11
		Total unspecified	**73**
Specified:			
SOC	**HLGT**	**PT**	
Cardiac	Cardiac Arrhythmias	AV block (n=1) Arrhythmia (n=2) Atrial fibrillation (n=2) Atrial flutter (n=1) Cardiac Arrest (n=20) Ventricular fibrillation (n=1) Acute Cardiac Event*(n=1) Cardiac Death** (n=3) Sudden cardiac death** (n=6)	37
	Cardiac Disorder	Cardiac Disorder (n=1) Cardiovascular Disorder (n=1)	2
	Cardiac Valve Disorders	Aortic Valve Stenosis (n=2)	2
	Coronary Artery Disorders	Acute Coronary Syndrome (n=1) Acute Myocardial Infarction (n=1) Myocardial Infarction (n=8)	10
	Heart Failures	Acute Cardiac Failure (n=2)) Cardiac Failure (n=15) Cardiac Asthma (n=2) Cardiogenic Shock (n=4) Cardiopulmonary Failure (n=1)	24
		Total Cardiac	**75**
Nervous System	Central Nervous System Vascular	Basilar Artery Thrombosis (n=2) Cerebral Infarction (n=3) Cerebral Hemorrhage (n=8) Cerebrovascular Accident (n=7) Ischemic Cerebral Infarction (n=6)	26

	Encephalopathies	Hyperammonaemic encephalopathy (n=1) Postresuscitation encephalopathy (n=1)	2
	Headaches	Headache	1
	Mental Impairment Disorders	Alzheimer's type dementia (n=1) Dementia (n=2)	3
	Seizures	Epilepsy	2
		Total Nervous System	**34**
Infections and infestations			
	Infections pathogen unspecified	Bronchitis (n=1) Infection (n=1) Pneumonia (n=12) Respiratory Tract Infection (n=2) Sepsis (n=1)	17
	Viral infections	COVID-19 (n=7) COVID-19 Pneumonia(n=2) Viral infection (n=1)	10
		Total Infections and infestations	**27**
Respiratory, thoracic mediastinal	Bronchial Disorders	Asthma	1
	Lower Respiratory Tract Disorders	Aspiration Pneumonia	4
	Pulmonary Vascular Disorders	Pulmonary Embolism	3
	Respiratory Disorders	Acute Respiratory Failure (n=1) Dyspnea (n=4) Hypoxia (n=1) Oxygen Saturation Decreased***(n=2) Respiratory Failure (n=3)	11
		Total Respiratory	**19**
Gastrointestinal	Gastrointestinal hemorrhages	Gastrointestinal Hemorrhage	4
	Gastrointestinal signs and symptoms	Acute Abdomen (n=1	1
	Gastrointestinal stenosis and obstruction	Ileus (n=1) Small Intestine Obstruction (n=1)	2

	Gastrointestinal vascular conditions	Intestinal Ischemia	1
	Malignant and unspecified neoplasms	Colon Cancer	1
		Total Gastrointestinal	**9**
OTHER			
Metabolism and nutritional	Appetite and general nutritional disorders	Cachexia (n=2) Decreased appetite (n=1) Hypophagia (n=3)	6
General disorders	Body temperature conditions	Hyperpyrexia (n=1) Pyrexia (n=1)	2
	General System Disorders	Chills (n=1) Multi Organ Failure (n=1)	2
Hepatobiliary disorders	Hepatic failure	Hepatic Coma (n=1) Hepatic Failure (n=1)	2
Injury, poisoning and procedural	Procedural related injuries	Vaccination complication	2
Renal and urinary disorders	Renal disorders	Azotemia	2
Blood and lymphatic system disorders	Hematological disorders	Hemophagocytic lymph histiocytosis	1
Psychiatric disorders	Deliria	Confusional State	1
Neoplasms	Plasma cell neoplasms	Plasma Cell Myeloma	1
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	Shock	1
		Total other	**20**

*not an official MedDra term ** primary SOC is “general disorders” *** primary SOC is “investigations”

4.3 Comorbidities and medication used per reported cause of death

Table 14 combines tables 8, 9 and 13.

Table 14 Comorbidities per reported cause of death-group level

Cause of Death	Medical history reported in this population	
Cardiac N=75 Av. Age 83,6	Cardiac Arrhythmias (n=28) Heart Failure (n=25) Cardiac Valve Disorders (n=9) Coronary Artery Disorders (n=3)	65
	Hypertension (n=20) Aneurysms (n=4) Arteriosclerosis, Claudication (n=3) Other vascular (n=4)	31
	Cardiac procedure (CABG, angioplasty, implantable defibrillator etc.	10
	CVA, Cerebral infarction, cerebral ischaemia , TIA (n=16) Vascular Parkinson, vascular dementia (n=4)	20
	Diabetes Mellitus	14
	COPD	8
	None of the above but medication indication CV disease	3
	None of the above but high BMI	1
	No information on medical history	3
	Number of people with none of the above	3
	Number of people with COVID 19 in medical history	9
Cause of Death	**Medical history reported in this population**	
"Unknown" "Death" N=62 Av. Age 84,1	Cardiac Arrhythmias (n=9) Heart Failure (n=9) Coronary Artery Disorders (n=2) Other Cardiac (n=2)	22
	Hypertension (n=8) Other vascular (n=4)	12
	Diabetes (n=9) Hyperlipidemia (n=1)	10
	None of the above but medication indicating CV disease	12
	Neoplasm (colon, breast, prostrate, non-Hodgkin, myelodysplastic syndrome)	6
	None of the above but dementia	6
	None of the above but other relevant history (Parkinson, COPD, COVID-19, opioid use)	6
	No information on medical history	4
	Number of people with none of the above	5
	Number of people with COVID 19 in medical history	9

Cause of Death	Medical history reported in this population	
Central Nervous System Vascular N=26 Av. Age 85,2	Cardiac Arrhythmias (n=8) Heart Failure (n=2) Coronary Artery Disorders (n=2) Other Cardiac (n=2)	14
	Hypertension (n=8) Other vascular (n=5)	13
	CVA, cerebral infarction, TIA	3
	Hypercholesterolemia, Diabetes Mellitus	5
	Neoplasms (Metastatic Prostrate, Pancreas carcinoma)	2
	None of the above but CV Medication	3
	No information on medical history	1
	Number of people with none of the above	3
	Number of people with COVID 19 in medical history	1
Cause of Death	**Medical history reported in this population**	
Pulmonary N=19 Av. Age 83,2	COPD	5
	Other respiratory	5
	GERD, Diaphragmatic hernia	3
	Atrial Fibrillation, Palpitations (n=5) Cardiac Failure (n=4) Coronary Artery Disorders (n=3) Aortic valve (n=1)	13
	Hypertension	5
	None of the above but Dementia or Parkinson	3
	None of the above but obesity, gastric bypass, TIA	2
	Number of people with none of the above	0
	Number of people with COVID 19 in medical history	5
Cause of Death	**Medical history reported in this population**	
Infectious N=27 Av. Age 85,8	Infection (n=1) COVID-19 (n=3) Cystitis/UTI (n=3) Bronchitis (n=2) Pneumonia/Resp tract (n=2) Already symptoms of infection prior to vaccination (n=1)	12
	Cardiac Arrythmia (n=4) Heart Failure (n=4) Cardiac Valve Disorder (n=2) Coronary Artery Disorder (n=3)	13
	Hypertension (n=7) Aneurysm (n=1)	8

	COPD (n=2) Pulmonary embolism, Emphysema, Pulmonary hypertension, Aspiration Pneumonia, Respiratory Failure	7
	Dementia (n=7) CVA, TIA (n=5) Parkinson(ism) n=3) Multi System Atrophy (n=1)	16
	Diabetes Mellitus	2
	No information on medical history	1
	Number of people with none of the above	3
	Number of people with COVID 19 in medical history	3
Cause of Death	**Medical history reported in this population**	
Sudden Death N=11 Av. age 83.1	Hypertension (n=5) Peripheral vascular disorder (n=1)	6
	Coronary artery disorder (n=3) Arrhythmias, defibrillator installed (n=2) Other cardiac disorder (n=2)	7
	Cerebrovascular accident	1
	None of the above but CV medication	2
	No medical history available	1
	Number of people with none of the above	1
	Number of people with COVID 19 in medical history	1
Cause of Death	**Medical history reported in this population**	
Gastro intestinal n=9 Av. Age 87.8	Abdominal discomfort, dysphagia, defecation disorder, inguinal hernia	4
	COVID 19, Diverticulitis	2
	Hypertension (n=3) Arteriosclerosis, infarction, intermittent claudication, peripheral artery disease, thrombosis	8
	Arrythmias (n=3) Coronary Artery Disease (n=2)	5
	Palliative	1
	Number of people with none of the above	1
	Number of people with COVID 19 in medical history	1

4.4 Causes of death in cases with prior COVID-19 infections

As described earlier there is a specific question on the reporting form related to having had a COVID-19 infection prior to vaccination. In 232/257 cases an answer was provided, which was “no” in 200 cases and “yes” in 32. In nine of these, cause of death was cardiac, 1 cerebrovascular. There were 8 causes of death related to the respiratory system: 5 (aspiration) pneumonia’s, 3 hypoxia/oxygen decrease. In 10 cases cause of death was not (yet) reported, the remaining 4 cases each had different causes of death unrelated to cardiac of pulmonary system reported.

4.5 Latency per cause of death

Figure 3 Latency per cause of death (exact latency known only)

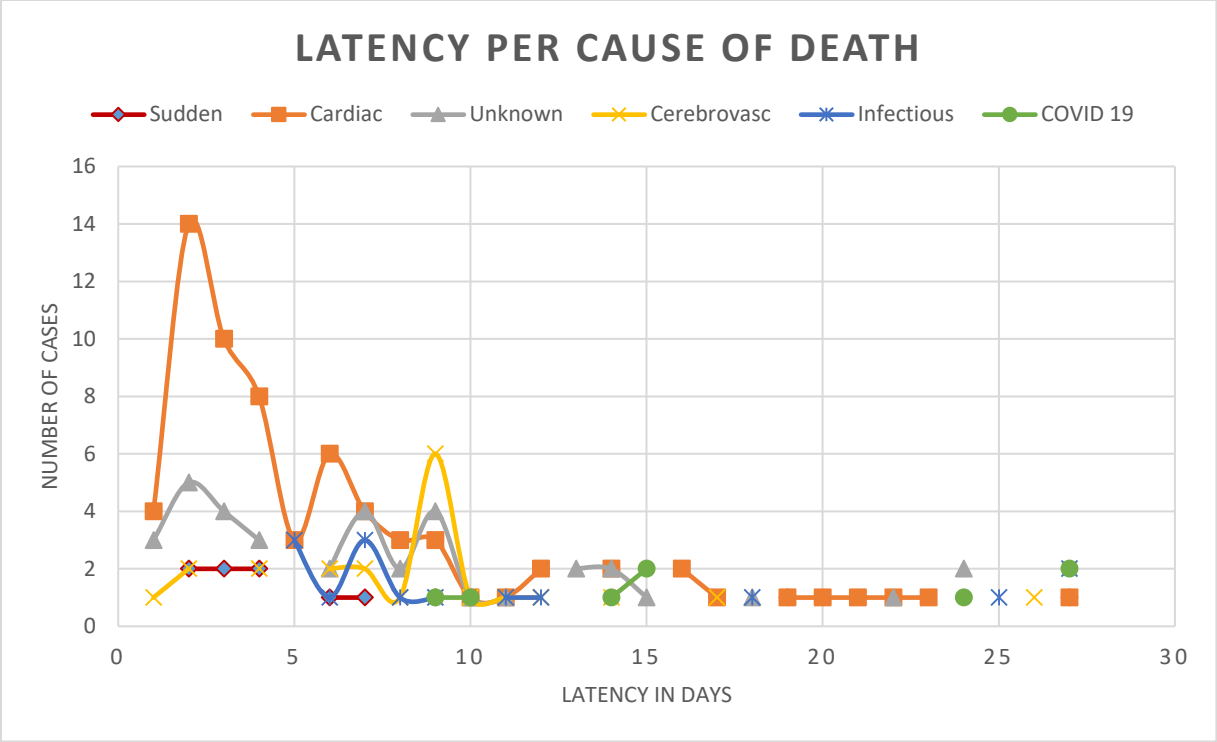

Table 15 Latency and causes of death, history and medication

Latency (days)	Number of reports	Reported causes of death*	Relevant Medical History**	Relevant Co-medication**
0-1	37 Av. Age 83.3	• 13x (sudden)death or unknown • 18x cardiac • 3x cerebrovascular • 3x other	• 23x cardio- and/or cerebrovascular medical history • 6x no reported CV history, but CV-medication • 13x diabetes mellitus	• 26x cardiovascular and/or antithrombotics • 3x opioids
2- 7	107 Av. Age 83.9	• 26x (sudden)death or unknown • 36 x cardiac • 11 x dyspnea, RTI, asthma, hypoxia, bronchitis • 8x (aspiration) pneumonia • 8x cerebrovascular	• 68 x cardiovascular and/or cerebrovascular medical history • 13 no reported CV history, but CV-medication • 22 x dementia	• 75x cardiovascular and/or antithrombotics • 6x opioids

		• 3x GI Hemorrhage and 1x ischemia • 14 x other	• 11 x diabetes mellitus	
8-14	62 Av. Age 83.61	• 20x (sudden)death or unknown • 10x cardiac • 10x cerebrovascular • 5x COVID-19 infectious • 4x (aspiration) Pneumonia • 2x Dementia • 11 x other	• 33 x cardiovascular and/or cerebrovascular • 7x no reported CV history, but CV-medication • 12x diabetes mellitus • 11x COPD or other respiratory • 10x neoplasm • 7x renal failure or impairment • 5x COVID-19 • 2x pneumonia	• 35x cardiovascular and/or antithrombotics • 6x opioids
>14	51 Av. Age 83.9	• 14 x (sudden) death or unknown • 11 x cardiac • 5 x cerebrovascular • 4x COVID-19 • 4x pneumonia • 3x pulmonary embolism • 3 x resp failure/ O2 saturation decreased/dyspnea • 7x other	• 27 x cardiovascular and/or cerebrovascular • 5 x diabetes mellitus • 5x neoplasms • 4x COPD or other respiratory • 3x renal impairment/failure	• 29 x cardiovascular and/or antithrombotics • 6x opioids

* mutually exclusive, ** not mutually exclusive

5.Assessment of potential causality

5.1 Method of assessment

All reports were assessed taken into account following aspects:

- latency time of events after vaccination
- the presence of a clear deterioration of a preexisting potentially fatal condition or occurrence of a new potentially fatal condition in the weeks prior to vaccination
- whether health events that occurred after vaccination could be attributed to the vaccination
- whether adverse events of the vaccination could have contributed to decompensation of an already vulnerable state

5.2 Outcome of assessments

5.2.1. Lack of information: 87 cases

In 35 reports an assessment was not possible, because Lareb was still awaiting follow up at the time of this overview. In the remaining 52 reports, based on the information that the reporter was able to collect and share with Lareb, a reasonable assessment was not possible.

5.2.2 Other causes more likely: 128 cases

These cases include patients in a fragile state on a downward slope, as well as patients that based on their medical history, risk factors and medication use were at very high risk to suffer from a (sudden) fatal event and/or patients in which the latency between vaccine and death was either very short or fairly long. In all these cases the contribution of the vaccination to the death could not be excluded but was deemed unlikely.

5.2.3 Adverse events may have contributed: 42

In these cases, the vaccination may have contributed to decompensation of an already vulnerable state.

In the large majority of these cases adverse events of reactogenicity, such as fever and nausea, are described by reporters as clear turning points in the patients' health state and may have contributed to the prelude of the fatal outcomes.

6. DISCUSSION

This overview was based on information received by Lareb with cut off April 15th, 2021, after 3.7 million COVID-19 vaccinations were administered and 264 reports of death after these vaccinations were received by Lareb. Although this may appear a small number on the total number of vaccinations, it is larger than anticipated, based on historical data. (e.g. influenza vaccination campaigns). The large attention in the media may have contributed to this. Also the Dutch RIVM LCI guideline encouraging health care professionals (HCP's) to report, even if causality is not clear, may have contributed to more health care professionals reports to Lareb. As such, Lareb is a proponent of the possibility for anybody to report with the lowest possible hurdle. However, as a consequence a fair share of reports do not contain enough details to be able to properly evaluate the case to make a reliable assessment. Therefore, after every report submitted to Lareb that included a fatal case, the reporter was contacted to ask for follow-up information. When this overview was written, follow up had not yet been obtained for all reports. In a substantial part of the cases, however, with or without follow up, a clear picture of what happened in the hours or even days prior to the death, and the primary cause of death is not available and these cases will remain not assessable.

A fatal outcome after vaccination does not imply a causal relationship. The background rate of mortality within the vaccinated age-group is relatively high. In the years prior to the pandemic, on average, every day 357 people aged 65+ years, including 228 of age 80+ died in the Netherlands, of all causes. Cardiovascular death was the leading cause of death in this age group, responsible for around 30% of fatalities.

In the large majority of assessable cases, vulnerable and often already progressively deteriorating health states and/or recent development of potentially fatal conditions unrelated to the vaccine, seem to be the most logical explanations for the cause of the events.

The cases present a large variety of disease courses, events before and after vaccination, and causes of death. They do not seem to point towards any unusual causes of death in this age range.

In a minority of the deceased reported, the vaccination caused adverse events that led to a clear bend in their health state. These adverse events, such as fever, nausea, malaise are in themselves not causes of death, but may have contributed to deterioration of an already vulnerable health state or condition.

At this moment in time, Lareb does not see any patterns that point towards serious adverse events for Covid-19 vaccines leading to a specific fatal outcome.

This signal has been raised on July 1, 2021. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl