

Supplementary Material

Unknown adverse drug reactions from spontaneous reports in Hospital setting: characterization, follow-up, and contribution to the pharmacovigilance system

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Supplementary table 1. Adverse drug reactions (ADRs)

Adverse drug reaction	N	%
Pemphigoid (3 aggravated)	7	2.4
Hepatic cytolysis	6	2
Cutaneous vasculitis	6	2
Fetal growth restriction	6	2
Sudden death	6	2
Distributive shock	5	1.7
Foetal death	5	1.7
Herpes zoster	4	1.4
Mixed liver injury	4	1.4
Premature rupture of membranes	4	1.4
Ascites	3	1
Acute kidney injury	3	1
Cardiac failure	3	1
Deep vein thrombosis	3	1

Adverse drug reaction	N	%
Disseminated intravascular coagulation	3	1
Guillain-Barré syndrome	3	1
Hepatitis cholestatic	3	1
Hypertransaminasemia	3	1
Pancytopenia	3	1
Pulmonary embolism	3	1
Reversible posterior encephalopathy syndrome	3	1
Urticaria	3	1
Abortion spontaneous	2	0.7
Acute generalised exanthematous pustulosis	2	0.7
Agranulocytosis	2	0.7
Alopecia	2	0.7
Anticipatory anxiety	2	0.7
Atrial fibrillation	2	0.7
Atrioventricular block	2	0.7
Bradycardia	2	0.7
Cardiogenic shock	2	0.7
Cough	2	0.7
Depression	2	0.7
Ear pain	2	0.7
Encephalopahty	2	0.7
Eosinophilia	2	0.7
Generalized edema	2	0.7
Hepatitis fulminant	2	0.7
Hyperbilirubinaemia	2	0.7
Hypertension	2	0.7
Lymphopenia	2	0.7
Myalgia	2	0.7
Myeloid leukaemia	2	0.7
Myoclonus	2	0.7
Opsoclonus myoclonus	2	0.7
Parotid gland enlargement	2	0.7
Phlebitis	2	0.7
Pneumonitis	2	0.7
Pyrexia	2	0.7
Rash maculo-papular	2	0.7
Seronegative arthritis	2	0.7
Tachycardia	2	0.7
Tendon disorder	2	0.7
Thrombocytopenic purpura	2	0.7
Thrombotic microangiopathy	2	0.7
Tinnitus	2	0.7
Vasculitis necrotising	2	0.7
Ventricular tachycardia	2	0.7
Akathisia	1	0.3
Acute interstitial pneumonitis	1	0.3
Acute lymphocytic leukaemia	1	0.3
Acute pancreatitis	1	0.3

Adverse drug reaction	N	%
Acute respiratory failure	1	0.3
Aorta hypoplasia	1	0.3
Aphthous ulcer	1	0.3
Arnold-Chiari malformation	1	0.3
Arthralgia	1	0.3
Asthenia	1	0.3
Ataxia	1	0.3
Atrial septal defect	1	0.3
Autoimmune hepatitis	1	0.3
Bronchospasm	1	0.3
Cardiac tamponade	1	0.3
Cardiomegaly	1	0.3
Cerebral infarction	1	0.3
Child apnea	1	0.3
Cholestasis	1	0.3
Chronic gastritis	1	0.3
Clostridium difficile colitis	1	0.3
Clot retraction abnormal	1	0.3
Colitis	1	0.3
Confusional state	1	0.3
Congenital anomaly SNC	1	0.3
Congenital pulmonary valve atresia	1	0.3
Congenital tricuspid valve stenosis	1	0.3
Cutaneous leishmaniasis	1	0.3
Cytokine storm	1	0.3
Delirium	1	0.3
Depressed level of consciousness	1	0.3
Desmoid tumour	1	0.3
Disseminated tuberculosis	1	0.3
Dysphoria	1	0.3
Dyspnea	1	0.3
Embryonal rhabdomyosarcoma	1	0.3
Erythema nodosum	1	0.3
Esophageal atresia	1	0.3
Extrasystoles	1	0.3
Facial asymmetry	1	0.3
Fatigue	1	0.3
Fixed eruption	1	0.3
Granulomatous dermatitis	1	0.3
Granulomatous liver disease	1	0.3
Haemophagocytic lymphohistiocytosis	1	0.3
Henoch-Schonlein purpura	1	0.3
Hepatitis	1	0.3
Hepatocellular injury	1	0.3
Hepatotoxicidad	1	0.3
Histiocytic necrotising lymphadenitis	1	0.3
Holoprosencephaly	1	0.3
Horner's syndrome	1	0.3

Adverse drug reaction	N	%
Hyperlipidaemia	1	0.3
Hyperthyroidism	1	0.3
Hypertriglyceridemia	1	0.3
Hypoacusis	1	0.3
Hyponatraemia	1	0.3
International normalised ratio increased	1	0.3
Interruption of aortic arch	1	0.3
Intestinal atresia	1	0.3
Intestinal haematoma	1	0.3
Intestinal malrotation	1	0.3
Intestinal perforation	1	0.3
Intra-abdominal haematoma	1	0.3
Kidney transplant rejection	1	0.3
Lactic acidosis	1	0.3
Lens dislocation	1	0.3
Leukoencephalopathy	1	0.3
Lichen planus	1	0.3
Liver transplant rejection	1	0.3
Long QT syndrome	1	0.3
Meconium peritonitis	1	0.3
Megaloblastic anemia	1	0.3
Meningitis aseptic	1	0.3
Meningomyelocele	1	0.3
Metabolic acidosis	1	0.3
Muscle contractions involuntary	1	0.3
Muscle rigidity	1	0.3
Muscle spasms	1	0.3
Musculoskeletal chest pain	1	0.3
Myasthenia gravis	1	0.3
Myocarditis	1	0.3
Narrow anterior chamber angle	1	0.3
Neurogenic bladder	1	0.3
Odynophagia	1	0.3
Optic neuritis	1	0.3
Oral candidiasis	1	0.3
Oral herpes	1	0.3
Palpable purpura	1	0.3
Paresthesia	1	0.3
Pericardial effusion	1	0.3
Pericarditis	1	0.3
Peripheral edema	1	0.3
Peripheral ischaemia	1	0.3
Petechiae	1	0.3
Pleuropericarditis	1	0.3
Polyarthritis	1	0.3
Polydactyly	1	0.3
Polyneuropathy	1	0.3
Portal vein thrombosis	1	0.3

Adverse drug reaction	N	%
Proteinuria	1	0.3
Prothrombin time prolonged	1	0.3
Pseudocirrhosis	1	0.3
Pulmonary arterial hypertension	1	0.3
Pulmonary artery thrombosis	1	0.3
Purpura	1	0.3
Rash pruritic	1	0.3
Retinal vascular thrombosis	1	0.3
Retrograde amnesia	1	0.3
Rhabdomyolysis	1	0.3
Sepsis neonatal	1	0.3
Single umbilical artery	1	0.3
Somnolence	1	0.3
Splenic infarction	1	0.3
Status epilepticus	1	0.3
Subarachnoid hemorrhage	1	0.3
Suicide attempt	1	0.3
Supraventricular extrasystoles	1	0.3
Supraventricular tachycardia	1	0.3
Tachyarrhythmia	1	0.3
Thrombocytopenia	1	0.3
Thrombotic stroke	1	0.3
Toxic epidermal necrolysis	1	0.3
Vascular access site haemorrhage	1	0.3
Vasculitis	1	0.3
Ventricular dilatation	1	0.3
Ventricular hypertrophy	1	0.3
Ventricular hypoplasia	1	0.3
Ventricular septal defect	1	0.3
Visceral leishmaniasis	1	0.3
Vocal cord paralysis	1	0.3
Vomiting	1	0.3
Vulvovaginal inflammation	1	0.3
Vulvovaginal pruritus	1	0.3
Total	295	100

Supplementary table 2. Drugs involved in unknown drug-ADR pairs

Drugs	N	%
Covid-19 vaccines	51	16
Hydroxychloroquine	7	2,2
Azithromycin	6	1,9
Pneumococcus, purified polysaccharides antigen conjugated	6	1,9
Lamotrigine	5	1,6
Paclitaxel	5	1,6
Ticagrelor	5	1,6
Valproic acid	5	1,6
Meningococcus B, multicomponent vaccine	4	1,3
Methotrexate	4	1,3
Metoclopramide	4	1,3
Oseltamivir	4	1,3
Proguanil/atovaquone	4	1,3
Sevoflurane	4	1,3
Tocilizumab	4	1,3
Trastuzumab emtansine	4	1,3
Vincristine	4	1,3
Acenocoumarol	3	0,9
Carboplatin	3	0,9
Ceftriaxone	3	0,9
Ciprofloxacin	3	0,9
Erenumab	3	0,9
Etanercept	3	0,9
Formoterol/budesonide	3	0,9
Furosemide	3	0,9
Galcanezumab	3	0,9
Infliximab	3	0,9
Lercanidipine	3	0,9
Metamizole sodium	3	0,9
Methylprednisolone	3	0,9
Ondansetron	3	0,9
Procarbazine	3	0,9
Repaglinide	3	0,9
Sugammadex	3	0,9
Adalimumab	2	0,6
Alemtuzumab	2	0,6
Anakinra	2	0,6
Azathioprine	2	0,6
Bisoprolol	2	0,6
Botulinum toxin	2	0,6
Daptomicin	2	0,6
Dimethyl fumarate	2	0,6
Disulfiram	2	0,6
Doxazosin	2	0,6
Esmolol	2	0,6
Esomeprazole	2	0,6

Drugs	N	%
Gabapentin	2	0,6
Glatiramer acetate	2	0,6
Ibrutinib	2	0,6
Influenza, inactivated, split virus or surface antigen	2	0,6
Levonorgestrel	2	0,6
Lidocaine	2	0,6
Lopinavir/ritonavir	2	0,6
Mirabegron	2	0,6
Octreotide	2	0,6
Oxaliplatin	2	0,6
Pemetrexed	2	0,6
Prednisone	2	0,6
Propofol	2	0,6
Ranibizumab	2	0,6
Salbutamol	2	0,6
Sirolimus	2	0,6
Somatropin	2	0,6
Tacrolimus	2	0,6
Teriflunomide	2	0,6
Thalidomide	2	0,6
Abemaciclib	1	0,3
Aciclovir	1	0,3
Acitretin	1	0,3
Amiodarone	1	0,3
Apixaban	1	0,3
Argatroban	1	0,3
Bevacizumab	1	0,3
Bosentan	1	0,3
Brexucabtagene autoleucel	1	0,3
Bupivacaine	1	0,3
Canagliflozin	1	0,3
Carbimazole	1	0,3
Carbocisteine	1	0,3
Ceftolozane/beta-lactamase inhibitor	1	0,3
Cefuroxime	1	0,3
Clonazepam	1	0,3
Clonidine	1	0,3
Colchicine	1	0,3
Dabrafenib	1	0,3
Dapagliflozin	1	0,3
Darunavir/cobicistat	1	0,3
Deoxycholic acid	1	0,3
Dexamethasone	1	0,3
Dexketoprofen	1	0,3
Diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B	1	0,3
Diphtheria-pertussis-poliomyelitis-tetanus	1	0,3
Edoxaban	1	0,3

Drugs	N	%
Enalapril	1	0,3
Enoxaparin	1	0,3
Eplerenone	1	0,3
Escitalopram	1	0,3
Fingolimod	1	0,3
Gemcitabine	1	0,3
Gliclazide	1	0,3
Haloperidol	1	0,3
Hepatitis A, inactivated, whole virus	1	0,3
Hydrochlorothiazide	1	0,3
Immunoglobulins, normal human, for intravascular administration.	1	0,3
Isoniazid	1	0,3
Lacosamide	1	0,3
Lamivudine/abacavir/dolutegravir	1	0,3
Lenalidomide	1	0,3
Levofloxacin	1	0,3
Measles, combinations with mumps and rubella, live attenuated	1	0,3
Megestrol	1	0,3
Mesalazine	1	0,3
Mycophenolic acid	1	0,3
Natalizumab	1	0,3
Nomegestrol/estradiol	1	0,3
Ocrelizumab	1	0,3
Olanzapine	1	0,3
Omeprazole	1	0,3
Opium derivatives/expectorants	1	0,3
Pantoprazole	1	0,3
Pegaspargase	1	0,3
Pembrolizumab	1	0,3
Piperacillin/beta-lactamase inhibitor	1	0,3
Pyrimethamine	1	0,3
Raltitrexed	1	0,3
Ranitidine	1	0,3
Retigabine	1	0,3
Risperidone	1	0,3
Rituximab	1	0,3
Rivaroxaban	1	0,3
Rota virus, live attenuated	1	0,3
Sertraline	1	0,3
Simvastatin	1	0,3
Sodium acetate	1	0,3
Sulfamethoxazole/trimethoprim	1	0,3
Teicoplanin	1	0,3
Tigecycline	1	0,3
Tofacitinib	1	0,3
Tramadol/paracetamol	1	0,3
Trametinib	1	0,3

Drugs	N	%
Ulipristal	1	0,3
Valsartan/sacubitril	1	0,3
Vedolizumab	1	0,3
Vortioxetine	1	0,3
Total	319	100

Supplementary table 3. Unknown drug-ADR pairs

System Organ Class, n (%) ADR (n)	Drugs involved (n)	Covid drugs involved (n)
Skin and subcutaneous tissue disorders, 34 (11.5)		
Pemphigoid (7)	repaglinide (2); risperidone (1); rota virus, live attenuated (1); diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B (1); pneumococcus, purified polysaccharides antigen conjugated (1); vortioxetine (1); meningococcus B, multicomponent vaccine (1)	
Cutaneous vasculitis (6)	metamizol sodium (2); cefuroxime (1); colchicine (1); dexketoprofen (1)	COVID-19 Vaccine (CHADOX1-S) (1)
Urticaria (3)	procarbazine (2); nomegestrol/estradiol (1)	
Alopecia (2)	isoniazide (1); rivaroxaban (1)	
Rash maculopapular (2)	sodium acetate (1); procarbazine (1)	COVID-19 Vaccine (tozinameran) (1)
Acute generalized exanthematous pustulosis (2)	mesalazine (2)	
Thrombocytopenic purpura (2)	disulfiram (1); valproic acid (1)	
Granulomatous dermatitis (1)	ibrutinib (1)	
Erythema nodosum (1)	pegaspargase (1)	
Fixed eruption (1)	pembrolizumab (1)	
Rash pruritic (1)	opium derivatives/expectorants (1)	
Lichen planus (1)		COVID-19 Vaccine (tozinameran) (1)
Toxic epidermal necrolysis (1)	pyrimethamine (1)	
Petechiae (1)	meningococcus B, multicomponent vaccine (1)	
Purpura (1)		COVID-19 Vaccine (tozinameran) (1)
Henoch-Schonlein purpura (1)		COVID-19 Vaccine (elasomeran) (1)
Palpable purpura (1)		COVID-19 Vaccine (CHADOX1-S) (1)
Cardiac disorders, 28 (9.5)		
Cardiac failure (3)	sirolimus (1)	COVID-19 Vaccine (tozinameran) (2)
Atrioventricular block (2)	bisoprolol, ticagrelor (interaction) (1); valproic acid (1)	
Bradycardia (2)	lamotrigine (1); Pneumococcus, purified polysaccharides antigen conjugated (1)	
Atrial fibrillation (2)	edoxaban (1)	COVID-19 Vaccine (CHADOX1-S) (1)
Cardiogenic shock (2)	prednisone (1)	Hydroxychloroquine, azithromycin (interaction) (1)
Tachycardia (2)	botulinum toxin (1); meningococcus B, multicomponent vaccine (1)	
Ventricular tachycardia (2)	eplerenone (1); valsartan/sacubitril (1)	

System Organ Class, n (%) ADR (n)	Drugs involved (n)	Covid drugs involved (n)
Cardiomegaly (1)	trastuzumab emtansine (1)	
Pericardial effusion (1)	thalidomide (1)	
Ventricular dilatation (1)	proguanil/atovaquone (1)	
Extrasystoles (1)		COVID-19 Vaccine (tozinameran) (1)
Supraventricular extrasystoles (1)		COVID-19 Vaccine (tozinameran) (1)
Ventricular hypertrophy (1)	trastuzumab emtansine (1)	
Myocarditis (1)	prednisone (1)	
Pericarditis (1)	ulipristal (1)	
Pleuropericarditis (1)		COVID-19 Vaccine (CHADOX1-S)
Long QT syndrome (1)		hydroxychloroquine, azithromycin, metoclopramide, propofol, salbutamol (interaction) (1)
Cardiac tamponade (1)	thalidomide (1)	
Tachyarrhythmia (1)		hydroxychloroquine, azithromycin (interaction) (1)
Supraventricular tachycardia (1)		COVID-19 Vaccine (tozinameran) (1)
Hepatobiliary disorders, 28 (9.5)		
Hepatic cytolysis (6)	bevacizumab (1); dexamethasone (1); lidocaine (1); sugammadex (1); ticagrelor (1); vincristine (1)	
Mixed liver injury (4)	clonidine (1); metamizole sodium (1); teriflunomide (1); ticagrelor (1)	
Hepatitis cholestatic (3)	canagliflozine (1); dapagliflozine (1); ticagrelor (1)	
Hypertransaminasemia (3)	vincristine (3)	
Hepatitis fulminant (2)	repaglinide (2)	COVID-19 Vaccine (Moderna) (1)
Hyperbilirubinaemia (2)	esmolol (1); ticagrelor (1)	
Cholestasis (1)	bosentan (1)	
Granulomatous liver disease (1)	ibrutinib (1)	
Hepatitis (1)	glatiramer acetate (1)	
Autoimmune hepatitis (1)		COVID-19 Vaccine (tozinameran) (1)
Hepatotoxicity (1)	esmolol (1)	
Hepatocellular injury (1)	abemaciclib (1)	
Pseudocirrhosis (1)	paclitaxel (1)	
Portal vein thrombosis (1)		COVID-19 Vaccine (tozinameran) (1)
Nervous system disorders, 27 (9.2)		
Reversible posterior encephalopathy syndrome (3)	lenalidomide (1); immunoglobulins, normal human, for intravascular administration (1)	methylprednisolone (1)

System Organ Class, n (%) ADR (n)	Drugs involved (n)	Covid drugs involved (n)
Guillain-Barré syndrome (3)	oxaliplati (1); raltitrexed (1); hepatitis A, inactivated, whole virus (1)	
Encephalopahty (2)	ceftriaxone (2)	
Myoclonus (2)	esomeprazole (1); sugammadex (1)	
Akathisia (1)	esomeprazole (1)	
Retrograde amnesia (1)	ciprofloxacin (1)	
Ataxia (1)	pneumococcus, purified polysaccharides antigen conjugated (1)	
Muscle contractions involuntary (1)		COVID-19 Vaccine (tozinameran) (1)
Status epilepticus (1)	Piperacillin/beta-lactamase inhibitor (1)	
Subarachnoid hemorrhage (1)	ciprofloxacin (1)	
Thrombotic stroke (1)		COVID-19 Vaccine (CHADOX1-S) (1)
Cerebral infarction (1)	galcanezumab (1)	
Leukoencephalopathy (1)	aciclovir (1)	
Myasthenia gravis (1)	alemtuzumab (1)	
Optic neuritis (1)		COVID-19 Vaccine (CHADOX1-S) (1)
Depressed level of consciousness (1)	carbocisteine (1)	
Vocal cord paralysis (1)		COVID-19 Vaccine (tozinameran) (1)
Paresthesia (1)		COVID-19 Vaccine (tozinameran) (1)
Polyneuropathy (1)		COVID-19 Vaccine (AD26) (1)
Horner's syndrome (1)	bupivacaine (1)	
Somnolence (1)		COVID-19 Vaccine (tozinameran) (1)
Blood and lymphatic system disorders, 17 (5.8)		
Disseminated intravascular coagulation (3)	dabrafenib (1); tigecicline (1); trametinib (1)	
Pancytopenia (3)	doxazosin (1); natalizumab (1)	COVID-19 Vaccine (elasomeran) (1)
Agranulocytosis (2)	argatroban (1); daptomicyn (1)	
Eosinophilia (2)	amiodarone (1); pantoprazol (1)	
Lymphopenia (2)	meningococcus b, multicomponent vaccine (1)	COVID-19 Vaccine (tozinameran) (1)
Thrombotic microangiopathy (2)	methylprednisolone (1); mycophenolic acid (1)	
Megaloblastic anemia (1)	gabapentin (1)	
Splenic infarction (1)		COVID-19 Vaccine (CHADOX1-S) (1)
Thrombocytopenia (1)		COVID-19 Vaccine (tozinameran) (1)
Pregnancy, puerperium and perinatal condition, 17 (5.8)		

System Organ Class, n (%) ADR (n)	Drugs involved (n)	Covid drugs involved (n)
Fetal growth restriction (6)	ondansetron (2); metoclopramide (1); diphtheria-pertussis-poliomyelitis-tetanus (1); ranitidine (1); influenza, inactivated, split virus or surface antigen (1)	
Fetal death (5)	clonazepam (1); haloperidol (1); lamotrigine (1); sertraline (1); valproic acid (1)	
Premature rupture of membranes (4)	azathioprine (1); escitalopram (1); infliximab (1); olanzapine (1)	
Abortion spontaneous (2)	sirolimus (1); tacrolimus (1)	
Gastrointestinal disorders, 16 (5.4)		
Ascites (3)	lecarnidipine (2); oseltamivir (1)	
Parotid gland enlargement (2)	somatropin (1); valproic acid (1)	
Intestinal atresia (1)	methotrexate (1)	
Colitis (1)	ocrelizumab (1)	
Chronic gastritis (1)	methotrexate (1)	
Intestinal haematoma (1)		COVID-19 Vaccine (elasomeran) (1)
Intra-abdominal haematoma (1)	acenocoumarol, megestrol, omeprazole (interaction) (1)	
Odynophagia (1)		COVID-19 Vaccine (tozinameran) (1)
Acute pancreatitis (1)	tocilizumab (1)	
Intestinal perforation (1)	oseltamivir (1)	
Meconium peritonitis (1)	oseltamivir (1)	
Aphthous ulcer (1)	mirabegron (1)	
Vomiting (1)	anakinra (1)	
Vascular disorders, 16 (5.4)		
Distributive shock (5)	bisoprolol (1); enalapril (1); furosemide (1); hydrochlorothiazide (1); tocilizumab (1)	
Deep vein thrombosis (3)		COVID-19 Vaccine (tozinameran) (1); COVID-19 Vaccine (CHADOX1-S) (1); COVID-19 Vaccine (AD26) (1)
Phlebitis (2)		COVID-19 Vaccine (tozinameran) (2)
Hypertension (2)	acitretin (1)	COVID-19 Vaccine (elasomeran) (1)
Vasculitis necrotising (2)	carboplatin; paclitaxel	
Peripheral ischaemia (1)	gemcitabine	
Vasculitis (1)		COVID-19 Vaccine (AD26) (1)
Congenital, familial and genetic disorders, 15 (5.1)		
Congenital anomaly SNC (1)	proguanil/atovaquone (1)	
Single umbilical artery (1)	sevoflurane (1)	

System Organ Class, n (%) ADR (n)	Drugs involved (n)	Covid drugs involved (n)
Congenital pulmonary valve atresia (1)	formoterol/budesonide (1)	
Esophageal atresia (1)	proguanil/atovaquone (1)	
Atrial septal defect (1)	trastuzumab (1)	
Ventricular septal defect (1)	formoterol/budesonide (1)	
Congenital tricuspid valve stenosis (1)	formoterol/budesonide (1)	
Aorta hypoplasia (1)	trastuzumab (1)	
Ventricular hypoplasia (1)	lamotrigine (1)	
Holoprosencephaly (1)	sevoflurane (1)	
Interruption of aortic arch (1)	proguanil/atovaquone (1)	
Arnold-Chiari malformation (1)	lamotrigine (1)	
Intestinal malrotation (1)	oseltamivir (1)	
Meningomyelocele (1)	lamotrigine (1)	
Polydactyly (1)	sevoflurane (1)	
Respiratory, thoracic and mediastinal disorders, 14 (4.7)		
Pulmonary embolism (3)	lamivudine/abacavir/dolutegravir (1)	COVID-19 Vaccine (tozinameran) (1); COVID-19 Vaccine (CHADOX1-S) (1)
Pneumonitis (2)	disulfiram (1); valproic acid (1)	
Cough (2)	etanercept (1)	COVID-19 Vaccine (tozinameran) (1)
Bronchospasm (1)	paclitaxel (1)	
Pulmonary arterial hypertension (1)		COVID-19 Vaccine (tozinameran) (1)
Acute respiratory failure (1)	meningococcus B, multicomponent vaccine (1)	
Dyspnea (1)	etanercept (1)	
Acute interstitial pneumonitis (1)	daptomicyn (1)	
Child apnea (1)	pneumococcus, purified polysaccharides antigen conjugated (1)	
Pulmonars artery thrombosis (1)		COVID-19 Vaccine (CHADOX1-S) (1)
General disorders and administration site conditions, 13 (4.4)		
Sudden death (6)	adalimumab (1)	COVID-19 Vaccine (tozinameran) (1); hydroxychloroquine (1); hydroxychloroquine, azithromycin, metoclopramide, propofol, salbutamol (1); hydroxychloroquine, azithromycin, ceftriaxone, lopinavir/ritonavir (1); hydroxychloroquine, azithromycin, levofloxacin, lopinavir/ritonavir, tacrolimus (1)

System Organ Class, n (%) ADR (n)	Drugs involved (n)	Covid drugs involved (n)
Generalized edema (2)	lercanidipine (1); levonorgestrel (1)	
Pyrexia (2)	anakinra (1); doxazosin (1)	
Asthenia (1)	galcanezumab (1)	
Peripheral edema (1)	mirabegron (1)	
Fatigue (1)	erenumab (1)	
Musculoskeletal and connective tissue disorders, 13 (4.4)		
Seronegative arthritis (2)	influenza, inactivated, split virus or surface antigen (1)	COVID-19 Vaccine (tozinameran) (1)
Myalgia (2)	erenumab (1); galcanezumab (1)	
Tendon disorder (2)	carboplatin (1); paclitaxel (1)	
Facial asymmetry (1)	sevoflurane (1)	
Musculoskeletal chest pain (1)	etanercept (1)	
Muscle rigidity (1)	sugammadex (1)	
Arthralgia (1)	levonorgestrel (1)	
Rhabdomyolysis (1)	ciprofloxacin, simvastatin (interaction) (1)	
Polyarthritis (1)	carbimazole (1)	
Muscle spasms (1)	enoxaparin (1)	
Infections and infestation, 12 (4.1)		
Herpes zoster (4)	botulinum toxin (1)	COVID-19 Vaccine (tozinameran) (2); COVID-19 Vaccine (CHADOX1-S) (1)
Oral herpes (1)		COVID-19 Vaccine (tozinameran) (1)
Oral candidiasis (1)	erenumab (1)	
Clostridium difficile colitis (1)	vedolizumab (1)	
Visceral leishmaniasis (1)	fingolimod (1)	
Cutaneous leishmaniasis (1)	infliximab (1)	
Meningitis aseptic (1)	adalimumab (1)	
Disseminated tuberculosis (1)	azathioprine, infliximab (interaction) (1)	
Sepsis neonatal (1)	pneumococcus, purified polysaccharides antigen conjugated (1)	
Psychiatric disorder, 8 (32.7)		
Anticipatory anxiety (2)	gabapentin (1); tramadol/paracetamol (1)	
Depression (2)	brexucabtagene autoleucel (1); tozilizumab (1)	
Delirium (1)	teicoplanin (1)	
Dysphoria (1)	metoclopramide (1)	

System Organ Class, n (%) ADR (n)	Drugs involved (n)	Covid drugs involved (n)
Confusional state (1)	Ceftolozane/beta-lactamase inhibitor (1)	
Suicide attempt (1)	methotrexate (1)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps), 6 (2.0)		
Myeloid leukaemia (2)	carboplatin (1); paclitaxel (1)	
Acute lymphocytic leukaemia (1)	somatropin (1)	
Histiocytic necrotising lymphadenitis (1)	methotrexate (1)	
Embryonal rhabdomyosarcoma (1)	ondansetro (1)	
Desmoid tumour (1)	glatiramer acetate (1)	
Ear and labyrinth disorders, 5 (1.7)		
Tinnitus (2)	pemetrexed (1); tofacitinib (1)	
Ear pain (2)		COVID-19 Vaccine (tozinameran) (2)
Hypoacusis (1)	pemetrexed (1)	
Eye disorders, 5 (1.7)		
Opsoclonus myoclonus (2)	pneumococcus, purified polysaccharides antigen conjugated, measles, combinations with mumps and rubella, live attenuated (1)	
Narrow anterior chamber angle (1)	furosemide (1)	
Lens dislocation (1)	furosemide	
Retinal vascular thrombosis (1)		COVID-19 Vaccine (CHADOX1-S) (1)
Metabolism and nutrition disorder, 5 (1.7)		
Lactic acidosis (1)	darunavir/cobicistat (1)	
Metabolic acidosis (1)	sulfamethoxazole/trimethoprim (1)	
Hyperlipidaemia (1)	teriflunomide (1)	
Hypertriglyceridemia (1)	tocilizumab (1)	
Hyponatraemia (1)	lacosamide (1)	
Renal and urinary disorders, 5 (1.7)		
Acute kidney injury (3)	deoxycholic acid (1); glicazide (1); methylprednisolone (1)	
Proteinuria (1)	ranibizumab (1)	
Neurogenic bladder (1)	retigabine (1)	
Immune system disorders, 4 (1.4)		
Haemophagocytic lymphohistiocytosis (1)	alemtuzumab (1)	
Liver transplant rejection (1)		COVID-19 Vaccine (elasomeran) (1)
Kidney transplant rejection (1)	ranibizumab (1)	

System Organ Class, n (%)	Drugs involved (n)	Covid drugs involved (n)
ADR (n)		
Cytokine storm (1)	oxaliplati (1)	
Investigations, 3 (1.0)		
International normalised ratio increased (1)	acenocoumarol, octreotide (interaction) (1)	
Clot retraction abnormal (1)	apixaban (1)	
Prothrombin time prolonged (1)	lidocaine (1)	
Reproductive system and breast disorders, 2 (0.7)		
Vulvovaginal inflammation (1)	dimethyl fumarate (1)	
Vulvovaginal pruritus (1)	dimethyl fumarate (1)	
Endocrine disorders, 1 (0.3)		
Hyperthyroidism (1)	rituximab (1)	
Injury, poisoning and procedural complications, 1 (0.3)		
Vascular access site haemorrhage (1)	acenocoumarol, octreotide (interaction) (1)	

Supplementary table 4. Unknown drug-ADR pairs with mortal outcome

Drug involved	ADRs
	Time of initial report
Atovaquone/ proguanil	Congenital abnormality of the CNS
	Esophageal atresia
	Ventricular dilation
	Disruption of the aortic arch
Budesonide/formoterol	Pulmonary valve atresia
	Tricuspid valve stenosis
	Ventricular septal defect
Adalimumab	Sudden death
Tozinameran	Sudden death
Tozinameran	Pulmonary embolism
Ticagrelor	Hepatic cytolysis
	Hyperbilirubinemia
Lamotrigine	Ventricular hypoplasia
Sevoflurane	Single umbilical artery
	Facial asymmetry
	Holoprosencephaly
	Polydactyly
Azithromycin, hydroxychloroquine, levofloxacin, lopinavir/ritonavir, tacrolimus (interaction)	Sudden death
Lamotrigine	Meningomyelocele
	Arnolquiari
Azithromycin, hydroxychloroquine (interaction)	Tachyarrhythmia
Azithromycin, hydroxychloroquine (interaction)	Cardiogenic shock
Hydroxychloroquine sulfate	Sudden death
Azithromycin, hydroxychloroquine, metoclopramide, propofol, salbutamol (interaction)	Sudden death
Azithromycin, hydroxychloroquine, metoclopramide, propofol, salbutamol (interaction)	Long QT syndrome
Azithromycin, hydroxychloroquine, ceftriaxone, lopinavir/ritonavir (interaction)	Sudden death
Clonazepam	Fetal death
Haloperidol	Fetal death
Lamotrigine	Fetal death
Sertraline	Fetal death
Sodium valproate	Fetal death
Prednisone	Cardiogenic shock
Prednisone	Myocarditis
	Time of follow-up

Lenalidomide

Posterior reversible encephalopathy
syndrome (PRES)

Methylprednisolone

Posterior reversible encephalopathy
syndrome (PRES)
