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## Review Article

## An Overview on the Epidemiology and Immunology of COVID-19

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## ABSTRACT

Coronaviruses are a large family of viruses that cause illnesses ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), and the 2019 novel coronavirus infection (COVID-19). Currently, there is no analyzed data to examine the outbreak of COVID-19 by continent and no determination of prevalence trends; this article reviews COVID-19 epidemiology and immunology. Original research, reviews, governmental databases, and treatment guidelines are analyzed to present the epidemiology and immunology of COVID-19. Reports from patients who were COVID-19 infected showed typical symptoms of neutrophilia, lymphopenia, and increased systemic inflammatory proteins of IL-6 and C reactive protein (CRP). These observations agree with the results of severe conditions of MERS or lethal cases of SARS, in which there is an increased presence of neutrophils and macrophages in the airways. Additionally, analyzed data showed that Europe (49.37%), the Americas (27.4%), and Eastern Mediterranean (10.07%) had the most cumulative total per 100,000 population confirmed cases, and Africa (6.9%), Western Pacific (3.46%), and South-East Asia (2.72%) had the lowest cumulative total per 100,000 population confirmed cases. In general, the trend lines showed that the number of confirmed cases (cumulative total) and deaths (cumulative total) would decrease eventually.

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**Abbreviation list:** MERS, Middle east respiratory syndrome; SARS, Severe acute respiratory syndrome; MERS-CoV, Middle east respiratory syndrome coronavirus; SARS-CoV, Severe acute respiratory syndrome coronavirus; COVID-19, Coronavirus disease 2019; CRP, C reactive protein; WHO, World health organization; PHEIC, Public health emergency of international concern; ACE2, Angiotensin-converting enzyme 2; PAMPs, Pathogen-associated molecular patterns; PRRs, Pattern recognition receptors; TLR-3, Toll-like receptors 3; RIG-I, Retinoic acid-inducible gene I; MDA5, Melanoma differentiation-associated protein 5; CXCL10, C-X-C motif chemokine 10; MCP-1, Monocyte chemoattractant protein 1; IP-10, Interferon gamma-induced protein 10; MIP, Macrophage inflammatory protein; ADE, Antibody-dependent enhancement; FcγR, Fcγ receptors; ARDS, Acute respiratory distress syndrome; HLH, Hemophagocytic lymphohistiocytosis.

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**Introduction**

In December 2019, unidentified pneumonia emerged in Wuhan, China, where many of the original patients had visited the seafood market of Wuhan. The isolation of the related virus from patients and subsequent molecular analyses indicated a 2019 novel coronavirus infection, which was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) [1,2,70]. The explosive growth of COVID-19 infection in January 2020 necessitated that the WHO declare this outbreak a public health emergency of international concern (PHEIC) [3,4].

Unfortunately, international travel spread the virus worldwide, and 192,284,207 confirmed cases, including 4,136,518 deaths, were reported by the WHO on 23 July 2021. After the shocking health threat from Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), a significant negative impact was felt on affected countries' economies. Searches on SARS-CoV showed a 'bat' origin and the transmission to humans via Himalayan palm civets (*Paguma larvata*) and raccoon dogs (*Nyctereutes procyonoides*) [5–8,71]. Afterward, the well-known Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged with rare transmission to humans with a higher fatality rate. Alpha and beta coronaviruses dispersed in China are mainly and naturally carried in bats. The study of the genetic diversity and molecular evolution of these coronaviruses has gained intense interest [9–11].

Due to the many human casualties caused by the COVID-19 in a short time around the world, many scientists sought to find the infection's mechanism and to collect the following demographic data. There is, however, no analyzed data to study the course of the disease and its prevalence trend. Therefore, this study reviewed COVID-19 epidemiology and immunology using original research, reviews, governmental databases, and treatment guidelines.

**Epidemiology of COVID-19**

The COVID-19 epidemic started with the first announcement on Feb. 20, 2020, of the fatalities (2239 cases) in China, including 75 cases on the mainland, 68 in Hong Kong, 10 in Macao, 26 in Taiwan, and the confirmed reports (1200 cases) elsewhere [12]. Three stages can roughly be observed from the epidemiology of COVID-19 (Fig. 1).

*Total information*

In the first stage, the epidemiologic analysis showed close contact was the key factor in-person-to-person transmission [13,14]. In the second stage, the reported cases outside Wuhan, in Beijing City and Guangdong indicated the spread of the virus, with the total number of infected cases rising to 205. Then 29 provinces of China and six countries conveyed 846 confirmed reports with an increase of 20 times faster than the first stage. Even though Wuhan's lockdown was implemented, more than 5 million people had already left Wuhan due to the Chinese New Year. In the third stage, 50–80% of all confirmed cases were clustered around Beijing, Shanghai, Jiangsu, and Shandong on Feb. 10, 2020 [15]. When the numbers increased 240 times and reached 9826 confirmed cases, the WHO

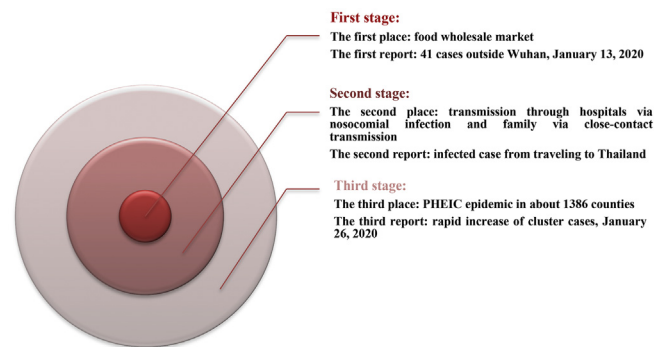


Fig. 1. Three stages of COVID-19 epidemiology.

declared PHEIC. About 44,730 infected cases and 16,067 suspected cases were recorded in 1386 counties and regions in China on Feb. 11, 2020 [16]. In this stage, the fatality rate was high in China (1114 reported deaths) and low outside China (one fatality in the Philippines). With the growth of new clinical definitions for diagnosis, the confirmed cases bounded to 14,840 in China. In contrast, 60,329 reported cases were recognized in 25 countries, with a 1471 times increase since the last report [15].

Regrettably, as of Feb. 11, 2020, 1716, medical-related staff from 422 medical institutions were infected. Among them, 64% were infected in Wuhan city and 23.3% in the rest of Hubei [17]. Preliminary evaluation of the dynamics of COVID-19 transmission indicated the basic reproductive number of about 1.4–3.9 for COVID-19 [18]. The R0 of SARS-CoV and MERS-CoV was 2.3–3.7 and 0.50–0.92 respectively in the absence of interventions [19]. The weekly operational reports of the WHO until July 23, 2021 is given in Table 1. The July 23, 2021 report of the WHO showed 192,284,207 confirmed cases of COVID-19, including 4,136,518 deaths.

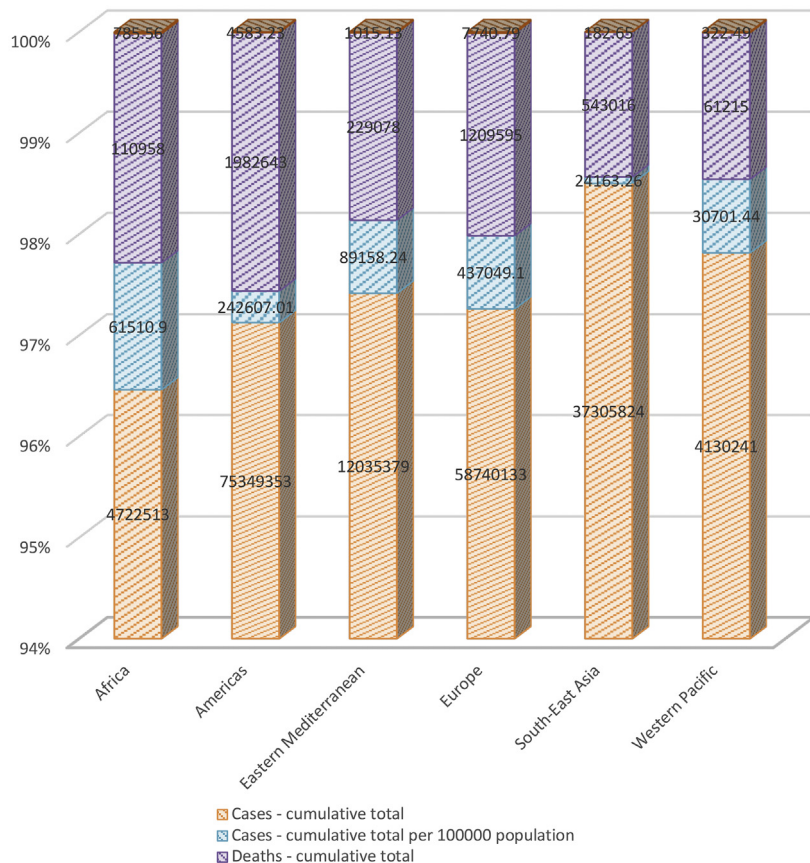
*Geographic distribution, confirmed cases, and related deaths*

Globally, over 192 million confirmed cases of COVID-19 were reported by the WHO until July 23, 2021. The updated data from confirmed cases and related deaths worldwide can be found on the WHO website. Since the first reports of cases from Wuhan at the end of 2019, cases have been reported in all continents except Antarctica. The number of confirmed cases and related deaths are reported in Table 2.

Table 3 shows that Europe (49.37%), the Americas (27.4%), and Eastern Mediterranean (10.07%) had the most cumulative total per 100,000 population confirmed cases until July 23, 2021, Africa (6.9%), Western Pacific (3.46%), and South-East Asia (2.72%) had the lowest cumulative total per 100,000 population confirmed cases. Until July 23, 2021, Europe (45.35%), the Americas (27.24%), and Africa (9.89%) had the most newly reported cases in the last seven days per 100,000 population confirmed cases. In the same period, Western Pacific (8.18%), Eastern Mediterranean (6.3%), and South-East Asia (3.01%) had the lowest newly reported cases in the last seven days per 100,000 population confirmed cases. Furthermore, Europe (52.91%), the Americas (31.32%), and Eastern Mediterranean (6.93%) had the most cumulative total per 100,000 population death

**Table 1**  
A short list of weekly WHO reports about COVID-19 ending Feb. 8, 2021.

Date of report	Confirmed cases	Deaths	Key Features
Dec. 7, 2020	66,243,918	1,528,984	<ol style="list-style-type: none"> <li>1. WHO calls for global solidarity to maintain HIV services.</li> <li>2. WHO and the Iraqi Governorate of Ninewa has established an isolation unit at Hamam Aleeel Field Hospital to treat suspected and confirmed cases of COVID-19.</li> <li>3. As of Dec. 4, 2020, The Solidarity Response Fund has raised or committed more than US\$ 238 million.</li> <li>4. WHO announced the recent launch of the Strategic Preparedness and Response Plan (SPRP) Monitoring and Evaluation Dashboard.</li> </ol>
Dec. 14, 2020	70,461,926	1,599,704	<ol style="list-style-type: none"> <li>1. Landmark alliance launches in Africa to fight COVID-19 misinformation.</li> <li>2. Nepal enhances laboratory capacity for COVID-19 and influenza.</li> <li>3. WHO's Contingency Fund for Emergencies (CFE) provided \$8.9 million for COVID-19 preparedness and response worldwide.</li> </ol>
Dec. 21, 2020	75,704,857	1,690,061	<ol style="list-style-type: none"> <li>1. PAHO prepares for COVID-19 vaccine deployment.</li> <li>2. Joint Intra-Action Review carried out in the Republic of Moldova in collaboration with the Ministry of Health Labour and Social Protection.</li> <li>3. WHO and IFRC sign a memorandum of understanding based on the EMT Initiative.</li> </ol>
Jan. 11, 2021	88,828,387	1,926,625	<ol style="list-style-type: none"> <li>1. As of Dec. 18, 2020, The Solidarity Response Fund has raised or committed more than US\$ 240 million.</li> <li>2. Islamic Republic of Iran tackles COVID-19 by enhancing primary health care.</li> <li>3. WHO Country Office in Montenegro supports COVID-19 response and continuity of essential health services.</li> </ol>
Jan. 19, 2021	93,956,883	2,029,084	<ol style="list-style-type: none"> <li>1. WHO supports the installation of public address systems at 50 remote health centers in Lao People's Democratic Republic.</li> <li>2. WHO SEAR countries gear up for massive vaccination campaign – this time for COVID-19 virus.</li> <li>3. US\$ 50 million Iran COVID-19 Emergency Response Project (ICERP) scales up nationwide response to the epidemic.</li> </ol>
Jan. 26, 2021	98,925,221	2 127,294	<ol style="list-style-type: none"> <li>1. WHO works with Romania's Ministry of Health and health professionals in the country to make telemedicine.</li> <li>2. WHO Afghanistan continues to strengthen COVID-19 testing capacity across the country.</li> <li>3. Vaccination Deployment Readiness map was launched on the Partners Platform.</li> </ol>
Feb. 1, 2021	102,399,513	2, 217,005	<ol style="list-style-type: none"> <li>1. The Pan American Health Organization (PAHO) launched a mobile application, MedPPE.</li> <li>2. WHO-led UN Crisis-Management Team coordinating 23 UN entities across nine areas of work.</li> <li>3. Mauritius conducts a COVID-19 vaccine simulation exercise before the national vaccine roll-out.</li> </ol>
Feb. 8, 2021	105,394,301	2,302,302	<ol style="list-style-type: none"> <li>1. WHO-led UN Crisis-Management Team coordinating 23 UN entities across nine areas of work.</li> <li>2. WHO launches EARS, an AI-powered public-access social listening tool.</li> <li>3. Countries submit vaccination plans for consideration of the next round of allocation.</li> </ol>



**Fig. 2.** The number of cumulative total confirmed cases and death cases, also, the number of cumulative total confirmed cases and death cases per 100,000 population, until July 23, 2021.

**Table 2**  
Geographic distribution, confirmed cases and related deaths as of July 23, 2021.

WHO Region	Country	Cases - cumulative total	CCT	CNR (7D)	CNRPP	CNR (24 h)	Deaths - cumulative total	DCT	DNR (7D)	DNRPP	DNR (24 h)
Africa	Algeria	158,213	360.8	8307	18.94	1208	4008	9.14	113	0.26	14
	Angola	41,405	125.98	875	2.66	178	977	2.97	26	0.08	4
	Benin	8324	68.66	80	0.66	80	107	0.88	0	0	0
	Botswana	97,657	4152.74	11,524	490.04	5755	1375	58.47	101	4.29	47
	Burkina Faso	13,537	64.76	7	0.03	0	169	0.81	0	0	0
	Burundi	6128	51.54	326	2.74	110	8	0.07	0	0	0
	Cabo Verde	33,452	6016.69	272	48.92	57	297	53.42	3	0.54	0
	Cameroon	81,871	308.41	404	1.52	0	1332	5.02	2	0.01	0
	Central African Republic	7147	147.98	5	0.1	0	98	2.03	0	0	0
	Chad	4965	30.23	6	0.04	0	174	1.06	0	0	0
	Comoros	4014	461.59	-58	-6.67	3	147	16.9	1	0.11	0
	Congo	13,117	237.71	184	3.33	0	176	3.19	4	0.07	0
	Côte d'Ivoire	49,386	187.22	387	1.47	98	324	1.23	5	0.02	2
	Democratic Republic of the Congo	47,174	52.67	1963	2.19	308	1021	1.14	37	0.04	1
	Equatorial Guinea	8848	630.66	20	1.43	0	123	8.77	0	0	0
	Eritrea	6480	182.72	98	2.76	7	32	0.9	2	0.06	0
	Eswatini	21,880	1885.94	1187	102.31	144	735	63.35	37	3.19	5
	Ethiopia	278,105	241.91	662	0.58	146	4363	3.8	13	0.01	3
	Gabon	25,309	1137.11	64	2.88	0	163	7.32	1	0.04	0
	Gambia	7161	296.32	551	22.8	0	197	8.15	9	0.37	0
	Ghana	100,250	322.63	2136	6.87	276	819	2.64	13	0.04	1
	Guinea	24,823	189.02	438	3.34	13	195	1.48	10	0.08	0
	Guinea-Bissau	4117	209.2	119	6.05	9	74	3.76	4	0.2	0
	Kenya	195,111	362.85	4091	7.61	801	3826	7.12	80	0.15	15
	Lesotho	12,679	591.85	526	24.55	49	357	16.66	19	0.89	8
	Liberia	5404	106.85	98	1.94	0	148	2.93	0	0	0
	Madagascar	42,631	153.95	114	0.41	3	941	3.4	5	0.02	0
	Malawi	46,417	242.64	4919	25.71	952	1410	7.37	109	0.57	21
	Mali	14,528	71.74	31	0.15	3	530	2.62	1	0	0
	Mauritania	23,223	499.46	1036	22.28	130	517	11.12	14	0.3	1
	Mauritius	3388	266.4	1024	80.52	207	19	1.49	1	0.08	0
	Mayotte	19,465	7134.87	14	5.13	5	174	63.78	0	0	0
	Mozambique	105,866	338.71	11,133	35.62	2153	1221	3.91	164	0.52	31
	Namibia	114,400	4502.33	5044	198.51	495	2665	104.88	395	15.55	45
	Niger	5594	23.11	39	0.16	0	195	0.81	1	0	1
	Nigeria	170,306	82.62	1232	0.6	184	2130	1.03	4	0	0
	Réunion	34,615	3866.25	1320	147.43	0	266	29.71	10	1.12	0
	Rwanda	61,375	473.86	9750	75.28	1309	704	5.44	88	0.68	11
	Saint Helena	0	0	0	0	0	0	0	0	0	0
	Sao Tome and Principe	2417	1102.85	17	7.76	0	37	16.88	0	0	0
	Senegal	54,820	327.4	6550	39.12	523	1256	7.5	47	0.28	10
	Seychelles	17,541	17835.83	307	312.16	0	79	80.33	11	11.18	0
	Sierra Leone	6206	77.8	84	1.05	5	117	1.47	4	0.05	1
	South Africa	234,2330	3949.39	89,090	150.21	14,858	68,625	115.71	2653	4.47	433
	South Sudan	10,917	97.53	0	0	0	117	1.05	0	0	0
	Togo	14,801	178.78	375	4.53	0	140	1.69	6	0.07	0
	Uganda	91,355	199.72	2275	4.97	193	2483	5.43	234	0.51	58
	United Republic of Tanzania	609	1.02	100	0.17	100	21	0.04	0	0	0
Zambia	189,731	1032.05	7602	41.35	1158	3196	17.38	205	1.12	34	
Zimbabwe	93,421	628.55	14,549	97.89	2301	2870	19.31	452	3.04	61	

Table 2 (Continued)

WHO Region	Country	Cases - cumulative total	CCT	CNR (7D)	CNRPP	CNR (24 h)	Deaths - cumulative total	DCT	DNR (7D)	DNRPP	DNR (24 h)
Americas	Anguilla	113	753.23	2	13.33	0	0	0	0	0	0
	Antigua and Barbuda	1277	1304.01	10	10.21	2	42	42.89	0	0	0
	Argentina	479,8851	10617.92	96,194	212.84	14,632	102,818	227.49	2568	5.68	437
	Aruba	11,271	10556.73	86	80.55	15	109	102.09	1	0.94	0
	Bahamas	13,781	3504.44	446	113.42	0	274	69.68	13	3.31	0
	Barbados	4302	1497	89	30.97	10	48	16.7	0	0	0
	Belize	13,865	3486.93	252	63.38	49	332	83.5	1	0.25	0
	Bermuda	2535	4070.79	8	12.85	0	33	52.99	0	0	0
	Bolivia (Plurinational State of)	465,351	3986.55	7139	61.16	1174	17,546	150.31	201	1.72	41
	Bonaire	1661	7941.67	25	119.53	2	17	81.28	0	0	0
	Brazil	19,473,954	9161.65	264,225	124.31	54,517	545,604	256.68	8210	3.86	1424
	British Virgin Islands	2210	7308.93	279	922.71	0	23	76.07	19	62.84	0
	Canada	1,424,715	3774.86	2884	7.64	495	26,512	70.25	54	0.14	4
	Cayman Islands	629	957.09	9	13.69	2	2	3.04	0	0	0
	Chile	160,4713	8394.52	10,217	53.45	1859	34,792	182	585	3.06	181
	Colombia	4,679,994	9197.58	114,622	225.27	11,244	117,482	230.89	3145	6.18	351
	Costa Rica	395,667	7767.13	8945	175.59	1532	4925	96.68	83	1.63	10
	Cuba	308,599	2724.55	45,513	401.82	7745	2137	18.87	411	3.63	65
	Curaçao	12,962	7899.18	509	310.19	79	126	76.79	0	0	0
	Dominica	209	290.31	10	13.89	3	0	0	0	0	0
	Dominican Republic	338,902	3124.12	2758	25.42	611	3931	36.24	24	0.22	2
	Ecuador	478,615	2712.77	5893	33.4	0	30,752	174.3	8880	50.33	0
	El Salvador	84,144	1297.28	1781	27.46	1292	2529	38.99	59	0.91	10
	Falkland Islands (Malvinas)	60	1722.65	0	0	0	0	0	0	0	0
	French Guiana	29,419	9849.61	705	236.04	134	170	56.92	7	2.34	1
	Grenada	165	146.64	2	1.78	0	1	0.89	0	0	0
	Guadeloupe	17,982	4494.11	173	43.24	0	278	69.48	4	1	0
	Guatemala	344,221	1921.35	16,466	91.91	3364	10,029	55.98	195	1.09	13
	Guyana	21,733	2763.07	510	64.84	65	515	65.48	12	1.53	1
	Haiti	19,762	173.31	135	1.18	0	523	4.59	11	0.1	0
	Honduras	284,187	2869.24	7198	72.67	1501	7535	76.08	179	1.81	28
	Jamaica	51,542	1740.6	629	21.24	138	1167	39.41	31	1.05	4
	Martinique	14,964	3987.58	2157	574.79	0	102	27.18	4	1.07	0
	Mexico	2,693,495	2089.07	76,668	59.46	15,198	237,207	183.98	1700	1.32	397
Montserrat	21	420.08	0	0	0	1	20	0	0	0	
Nicaragua	7313	110.39	269	4.06	0	194	2.93	1	0.02	0	
Panama	425,599	9863.78	6995	162.12	1144	6723	155.81	62	1.44	7	
Paraguay	447,146	6269.1	6090	85.38	879	14,446	202.54	380	5.33	52	
Peru	2,097,811	6362.43	11,928	36.18	1798	195,429	592.71	677	2.05	97	
Puerto Rico	142,359	4976.1	1259	44.01	180	2566	89.69	7	0.24	1	
Saba	7	362.13	0	0	0	0	0	0	0	0	
Saint Barthélemy	1057	10692.97	5	50.58	0	1	10.12	0	0	0	
Saint Kitts and Nevis	557	1047.15	13	24.44	0	3	5.64	0	0	0	
Saint Lucia	5496	2993.02	57	31.04	12	87	47.38	0	0	0	
Saint Martin	2523	6526.29	51	131.92	0	30	77.6	0	0	0	
Saint Pierre and Miquelon	28	483.18	2	34.51	1	0	0	0	0	0	
Saint Vincent and the Grenadines	2266	2042.55	8	7.21	3	12	10.82	0	0	0	
Sint Eustatius	20	637.15	0	0	0	0	0	0	0	0	
Sint Maarten	2695	6284.69	39	90.95	8	34	79.29	0	0	0	

Table 2 (Continued)

WHO Region	Country	Cases - cumulative total	CCT	CNR (7D)	CNRPP	CNR (24 h)	Deaths - cumulative total	DCT	DNR (7D)	DNRPP	DNR (24 h)
Eastern Mediterranean	Suriname	24,490	4174.68	774	131.94	55	625	106.54	28	4.77	5
	Trinidad and Tobago	36,626	2617.1	1390	99.32	272	1003	71.67	40	2.86	3
	Turks and Caicos Islands	2459	6351.05	15	38.74	1	18	46.49	0	0	0
	United States of America	33,875,385	10234.17	231,856	70.05	0	604,546	182.64	1376	0.42	0
	United States Virgin Islands	4286	4104.38	167	159.92	37	33	31.6	1	0.96	0
	Uruguay	379,613	10928.11	1909	54.96	237	5905	169.99	51	1.47	9
	Venezuela (Bolivarian Republic of)	295,746	1040.04	7647	26.89	1019	3426	12.05	99	0.35	18
	Afghanistan	143,439	368.47	4388	11.27	256	6357	16.33	285	0.73	32
	Bahrain	268,092	15755.52	473	27.8	0	1381	81.16	2	0.12	0
	Djibouti	11,628	1176.92	6	0.61	0	155	15.69	0	0	0
	Egypt	283,862	277.39	372	0.36	0	16,465	16.09	40	0.04	0
	Iran (Islamic Republic of)	3,623,840	4314.46	159,785	190.24	20,313	88,063	104.85	1471	1.75	226
	Iraq	1,526,943	3796.24	60,414	150.2	8106	18,101	45	394	0.98	81
	Jordan	762,706	7475.21	3020	29.6	0	9922	97.24	50	0.49	0
	Kuwait	388,881	9106.07	6797	159.16	0	2255	52.8	81	1.9	0
	Lebanon	552,328	8092.19	2901	42.5	0	7888	115.57	6	0.09	0
	Libya	227,433	3309.9	12,865	187.23	732	3322	48.35	73	1.06	13
	Morocco	566,356	1534.4	16,512	44.74	0	9498	25.73	80	0.22	0
	occupied Palestinian territory, including east Jerusalem	344,717	6757.28	372	7.29	0	3859	75.65	6	0.12	0
	Oman	289,042	5660.14	0	0	0	3498	68.5	0	0	0
Pakistan	998,609	452.08	17,402	7.88	2158	22,928	10.38	239	0.11	40	
Qatar	224,834	7803.88	923	32.04	196	600	20.83	1	0.03	0	
Saudi Arabia	514,446	1477.7	8321	23.9	1162	8130	23.35	95	0.27	15	
Somalia	15,162	95.4	77	0.48	0	781	4.91	0	0	0	
Sudan	37,138	84.69	0	0	0	2776	6.33	0	0	0	
Syrian Arab Republic	25,849	147.7	35	0.2	0	1905	10.89	3	0.02	0	
Tunisia	555,997	4704.42	29,510	249.69	0	17,913	151.57	904	7.65	0	
United Arab Emirates	667,080	6744.72	10,726	108.45	1547	1910	19.31	25	0.25	3	
Yemen	6997	23.46	30	0.1	0	1371	4.6	5	0.02	0	
Europe	Albania	132,797	4614.53	168	5.84	34	2456	85.34	0	0	0
	Andorra	14,464	18719.99	225	291.21	85	127	164.37	0	0	0
	Armenia	228,382	7707.19	1271	42.89	221	4579	154.53	21	0.71	4
	Austria	650,776	7311.22	2529	28.41	421	10,523	118.22	1	0.01	0
	Azerbaijan	339,274	3346.17	1473	14.53	212	4999	49.3	9	0.09	1
	Belarus	437,664	4631.7	6552	69.34	1069	3365	35.61	68	0.72	10
	Belgium	1,112,161	9652.13	7896	68.53	1	25,217	218.85	8	0.07	2
	Bosnia and Herzegovina	205,384	6260.15	117	3.57	39	9673	294.84	8	0.24	2
	Bulgaria	423,440	6091.36	643	9.25	121	18,189	261.66	26	0.37	2
	Croatia	362,305	8927.8	956	23.56	176	8245	203.17	11	0.27	0
	Cyprus	95,307	10732.71	6850	771.39	1046	398	44.82	15	1.69	4
	Czechia	1,672,140	15636.33	1557	14.56	207	30,347	283.78	12	0.11	0
	Denmark	309,420	5313.97	5951	102.2	805	2542	43.66	2	0.03	0
	Estonia	132,262	9952.17	519	39.05	83	1271	95.64	0	0	0
	Faroe Islands	958	1960.5	44	90.04	0	1	2.05	0	0	0

Table 2 (Continued)

WHO Region	Country	Cases - cumulative total	CCT	CNR (7D)	CNRPP	CNR (24 h)	Deaths - cumulative total	DCT	DNR (7D)	DNRPP	DNR (24 h)
	Finland	102,042	1846.82	2450	44.34	412	978	17.7	0	0	0
	France	5,813,457	8938.37	95,742	147.21	21,769	110,566	170	104	0.16	10
	Georgia	398,081	9979.03	13,694	343.28	2460	5656	141.78	140	3.51	20
	Germany	3,752,592	4512.13	10,811	13	2089	91,492	110.01	155	0.19	34
	Gibraltar	4704	13962.19	218	647.06	33	94	279.01	0	0	0
	Greece	469,042	4375.98	18,530	172.88	2601	12,875	120.12	56	0.52	5
	Greenland	85	149.72	19	33.47	1	0	0	0	0	0
	Guernsey	908	1408.45	47	72.9	4	17	26.37	0	0	0
	Holy See	26	3213.84	0	0	0	0	0	0	0	0
	Hungary	809,101	8281.89	376	3.85	85	30,020	307.28	5	0.05	0
	Iceland	6967	1913.31	249	68.38	0	30	8.24	0	0	0
	Ireland	289,139	5824.2	8355	168.3	1188	5026	101.24	8	0.16	0
	Isle of Man	2821	3317.57	1072	1260.7	182	29	34.1	0	0	0
	Israel	857,554	9907.57	7040	81.34	365	6457	74.6	12	0.14	0
	Italy	4,302,393	7213.76	24,074	40.36	5056	127,920	214.48	80	0.13	15
	Jersey	7077	6565.18	1837	1704.14	215	69	64.01	0	0	0
	Kazakhstan	568,915	3029.9	27,022	143.91	0	8538	45.47	365	1.94	0
	Kosovo [1]	107,911	6009.53	71	3.95	28	2255	125.58	1	0.06	0
	Kyrgyzstan	155,005	2375.85	8713	133.55	1127	2227	34.13	73	1.12	10
	Latvia	138,344	7251.97	303	15.88	44	2549	133.62	8	0.42	0
	Liechtenstein	3174	8191.6	13	33.55	0	58	149.69	0	0	0
	Lithuania	280,541	10040.51	969	34.68	245	4409	157.8	5	0.18	1
	Luxembourg	73,309	11708.68	677	108.13	94	821	131.13	2	0.32	0
	Malta	33,198	6451.68	1364	265.08	166	420	81.62	0	0	0
	Monaco	2744	6992.15	89	226.79	16	33	84.09	0	0	0
	Montenegro	100,854	16057.97	243	38.69	0	1624	258.57	3	0.48	0
	Netherlands	1,827,273	10496.99	61,457	353.05	6301	17,789	102.19	16	0.09	3
	North Macedonia	155,981	7486.92	115	5.52	16	5489	263.47	2	0.1	1
	Norway	135,234	2519.46	1358	25.3	265	799	14.89	3	0.06	0
	Poland	2,881,948	7592.44	707	1.86	108	75,235	198.21	30	0.08	4
	Portugal	943,244	9161.35	23,044	223.82	3622	17,248	167.52	61	0.59	16
	Republic of Moldova	258,365	6404.74	599	14.85	128	6236	154.59	17	0.42	4
	Romania	1,082,057	5598.15	518	2.68	104	34,266	177.28	12	0.06	1
	Russian Federation	6,078,522	4165.24	170,523	116.85	23,811	152,296	104.36	5428	3.72	795
	San Marino	5107	15048.03	13	38.31	0	90	265.19	0	0	0
	Serbia	719,462	10386.79	1369	19.76	228	7095	102.43	17	0.25	3
	Slovakia	392,259	7187.03	225	4.12	40	12,534	229.65	10	0.18	0
	Slovenia	258,467	12332.26	421	20.09	69	4761	227.16	0	0	0
	Spain	4,249,258	8977.44	155,222	327.94	17,218	81,194	171.54	76	0.16	3
	Sweden	109,6341	10615.65	2434	23.57	582	14,651	141.86	0	0	0
	Switzerland	708,703	8188.73	3636	42.01	5	10,329	119.35	1	0.01	0
	Tajikistan	14,761	154.77	316	3.31	0	117	1.23	6	0.06	0
	The United Kingdom	5,602,325	8252.55	321,223	473.18	39,315	128,980	189.99	387	0.57	84
	Turkey	5,563,903	6597.06	56,448	66.93	9586	50,761	60.19	346	0.41	52
	Turkmenistan	0	0	0	0	0	0	0	0	0	0
	Ukraine	2,247,419	5138.87	3814	8.72	763	52,811	120.76	109	0.25	21
	Uzbekistan	122,786	366.86	4406	13.16	738	819	2.45	30	0.09	5
South-East Asia	Bangladesh	1,146,564	696.2	62,642	38.04	6364	18,851	11.45	1386	0.84	166
	Bhutan	2470	320.11	72	9.33	12	2	0.26	0	0	0
	Democratic People's Republic of Korea	0	0	0	0	0	0	0	0	0	0
	India	31,293,062	2267.61	266,233	19.29	35,342	419,470	30.4	6939	0.5	483
	Indonesia	3,082,410	1126.93	301,607	110.27	49,071	80,598	29.47	9201	3.36	1566
	Maldives	76,454	14143.9	718	132.83	0	218	40.33	2	0.37	0
	Myanmar	258,870	475.78	40,131	73.76	5506	6459	11.87	1923	3.53	326



Table 2 (Continued)

WHO Region	Country	Cases - cumulative total	CCT	CNR (7D)	CNRPP	CNR (24 h)	Deaths - cumulative total	DCT	DNR (7D)	DNRPP	DNR (24 h)
Western Pacific	Nepal	676,708	2322.52	12,132	41.64	1982	9679	33.22	173	0.59	18
	Sri Lanka	291,298	1360.36	9238	43.14	0	3902	18.22	257	1.2	0
	Thailand	467,707	670.07	85,800	122.92	14,575	3811	5.46	712	1.02	114
	Timor-Leste	10,281	779.78	232	17.6	54	26	1.97	0	0	0
	American Samoa	0	0	0	0	0	0	0	0	0	0
	Australia	32,427	127.17	911	3.57	159	915	3.59	3	0.01	0
	Brunei Darussalam	311	71.09	29	6.63	2	3	0.69	0	0	0
	Cambodia	70,419	421.19	5808	34.74	811	1188	7.11	163	0.97	20
	China	120,000	8.16	461	0.03	82	5630	0.38	23	0	4
	Cook Islands	0	0	0	0	0	0	0	0	0	0
	Fiji	21,361	2382.86	7475	833.85	918	161	17.96	87	9.71	15
	French Polynesia	19,234	6847.08	176	62.65	39	145	51.62	1	0.36	1
	Guam	8231	4876.91	26	15.41	14	143	84.73	1	0.59	0
	Japan	857,799	678.23	26,606	21.04	5282	15,106	11.94	92	0.07	9
	Kiribati	0	0	0	0	0	0	0	0	0	0
	Lao People's Democratic Republic	4119	56.61	1027	14.12	256	5	0.07	1	0.01	0
	Malaysia	964,918	2981.27	84,136	259.95	13,034	7574	23.4	961	2.97	134
	Marshall Islands	4	6.76	0	0	0	0	0	0	0	0
	Micronesia (Federated States of)	0	0	0	0	0	0	0	0	0	0
	Mongolia	152,539	4653.01	9411	287.07	0	755	23.03	48	1.46	0
	Nauru	0	0	0	0	0	0	0	0	0	0
	New Caledonia	131	45.88	2	0.7	0	0	0	0	0	0
	New Zealand	2499	51.82	53	1.1	20	26	0.54	0	0	0
	Niue	0	0	0	0	0	0	0	0	0	0
	Northern Mariana Islands (Commonwealth of the)	188	326.63	1	1.74	0	2	3.47	0	0	0
	Palau	0	0	0	0	0	0	0	0	0	0
	Papua New Guinea	17,524	195.86	99	1.11	0	192	2.15	6	0.07	0
	Philippines	1,530,266	1396.47	39,614	36.15	5828	26,891	24.54	577	0.53	17
	Pitcairn Islands	0	0	0	0	0	0	0	0	0	0
	Republic of Korea	185,733	362.27	10,687	20.84	1630	2066	4.03	15	0.03	3
Samoa	1	0.5	0	0	0	0	0	0	0	0	
Singapore	63,791	1090.38	939	16.05	170	36	0.62	0	0	0	
Solomon Islands	20	2.91	0	0	0	0	0	0	0	0	
Tokelau	0	0	0	0	0	0	0	0	0	0	
Tonga	0	0	0	0	0	0	0	0	0	0	
Tuvalu	0	0	0	0	0	0	0	0	0	0	
Vanuatu	3	0.98	0	0	0	0	0	0	0	0	
Viet Nam	78,269	80.41	35,981	36.96	7125	370	0.38	163	0.17	0	
Wallis and Futuna	454	4036.99	0	0	0	7	62.24	0	0	0	
Other	Other	764		0		0	13		0		0
Total (Global)		192,284,207	2466.908864	3,533,643	45.33485	483,475	4,136,518	53.06943	68,246	0.875562	8366

CCT: Cases - cumulative total per 100,000 population, CNR (7D): Cases - newly reported in last seven days, CNRPP: Cases - newly reported in last seven days per 100,000 population, CNR (24 h): Cases - newly reported in last 24 h, DCT: Deaths - cumulative total per 100,000 population, DNR (7D): Deaths - newly reported in last seven days, DNRPP: Deaths - newly reported in last seven days per 100,000 population, DNR (24 h): Deaths - newly reported in last 24 h.

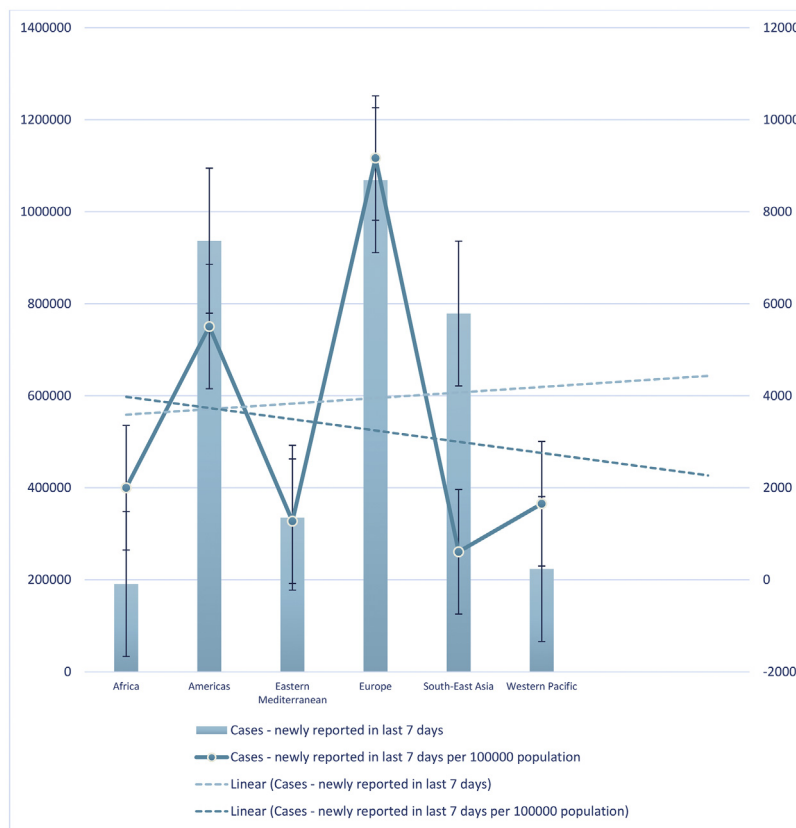


Fig. 3. The number of newly cumulative total cases and cumulative total cases per 100,000 population in the last seven days until July 23, 2021.

Table 3  
Global distribution of confirmed cases and related deaths until July 23, 2021.

WHO Region	Cases - cumulative total	CCT	CNR	CNRPP	Cases - newly reported in last 24 h	Deaths - cumulative total	DCT	DNR	DNRPP	Deaths - newly reported in last 24 h
Africa	4,722,513	61510.9	190,877	2000.1	33,821	110,958	785.56	4884	50.01	807
Americas	75,349,353	242,607	937,013	5504.45	121,309	1,982,643	4583.23	29,119	175.92	3161
Eastern Mediterranean	12,035,379	89158.24	334,929	1273.74	34,470	229,078	1015.13	3760	15.85	410
Europe	58,740,133	437049.1	1,068,577	9164.82	145,599	1,209,595	7740.79	7749	20.79	1112
South-East Asia	37,305,824	24163.26	778,805	608.82	112,906	543,016	182.65	20,593	11.41	2673
Western Pacific	4,130,241	30701.44	223,442	1653.71	35,370	61,215	322.49	2141	16.95	203
Total	192,283,443	885,190	3,533,643	20205.64	483,475	4,136,505	14629.85	68,246	290.93	8366

CCT: Cases - cumulative total per 100,000 population, CNR: Cases - newly reported in last seven days, CNRPP: Cases - newly reported in last seven days per 100,000 population, DCT: Deaths - cumulative total per 100,000 population, DNR: Deaths - newly reported in last seven days, DNRPP: Deaths - newly reported in last seven days per 100,000 population.

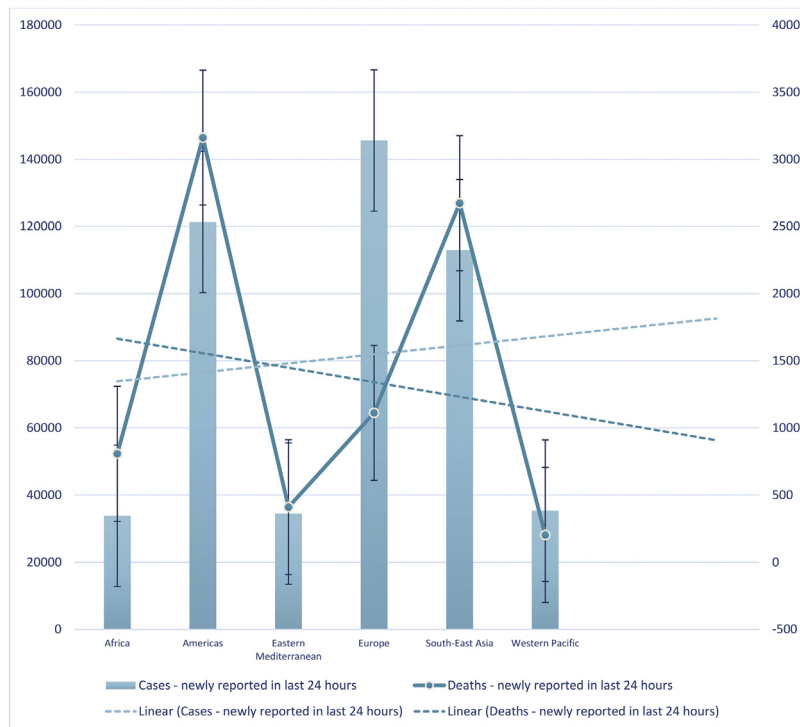
cases until July 23, 2021, Africa (5.36%), Western Pacific (2.2%), and South-East Asia (1.24%) had the lowest cumulative total per 100,000 population death cases. Until July 23, 2021, the Americas (60.46%), Africa (17.18%), and Europe (7.14%) had the most newly reported death cases in the last seven days per 100,000 population. In the same period, Western Pacific (5.82%), Eastern Mediterranean (5.44%), and South-East Asia (3.92%) had the lowest newly reported death cases in the last seven days per 100,000 population.

Notably, the confirmed cases-cumulative and confirmed cases-cumulative total per 100000 population in Africa, Eastern Mediterranean, Western Pacific, and Europe exhibited a raised trend in comparison to confirmed cases in the Americas and South-East Asia where the trend showed a fall. Concurrently, a similar trend for the death cases were also observed for all these continents (Fig. 2).

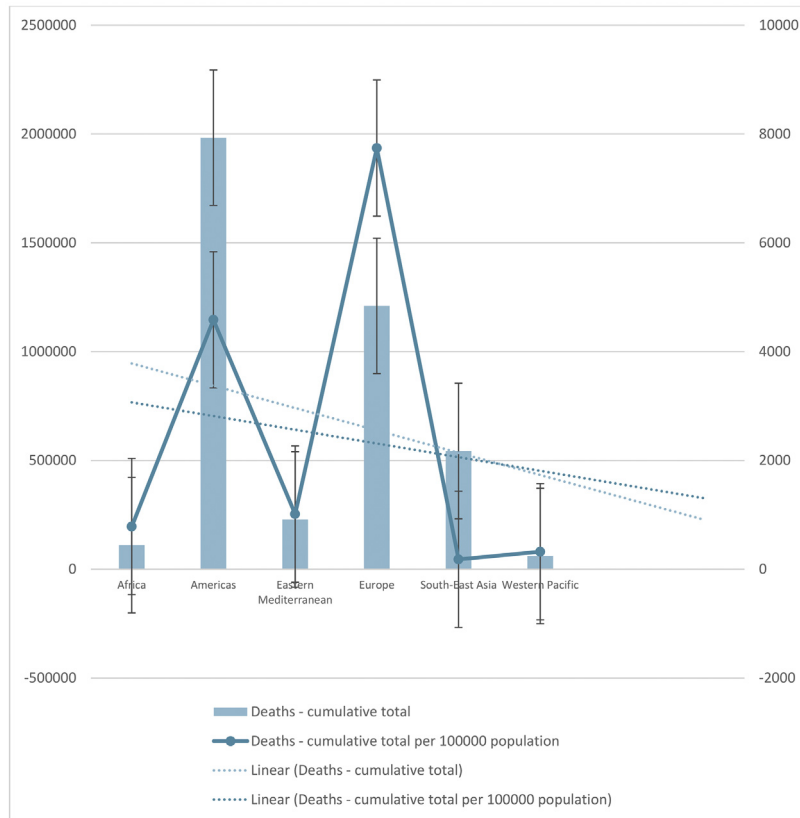
The trend lines in Fig. 3 shows that until July 23, 2021, the number of newly cumulative total cases and cumulative total cases per 100000 population in the last seven days increased and decreased,

respectively. In this period, Europe had the highest and South-East Asia had the lowest number of newly cumulative total cases and cumulative total cases per 100000 population in the last seven days.

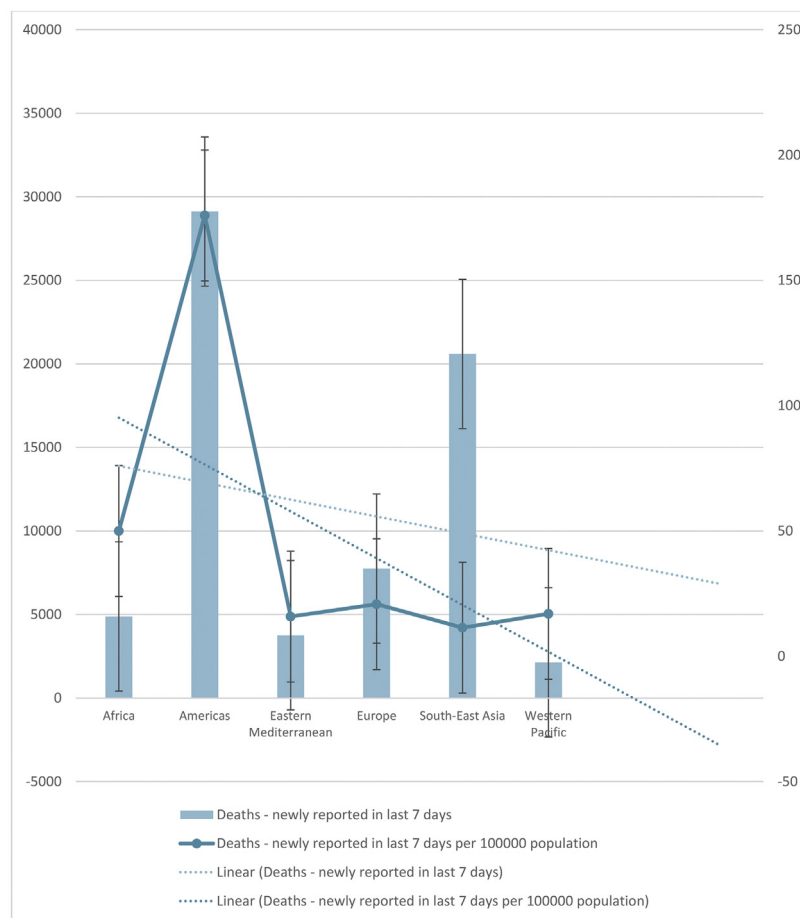
The trend line in Fig. 4 shows that until July 23, 2021, the number of newly reported cases in the last 24 h increased, and the number of newly reported deaths in the last 24 h decreased. Europe had the highest number of newly reported cases in the last 24 h while the Americas had the highest number of newly reported deaths in the last 24 h. Africa had the lowest number of newly reported cases, while the Western Pacific had the lowest number of newly reported deaths in the last 24 h. The trend line in Fig. 5 shows that until July 23, 2021, the number of newly cumulative total deaths and cumulative total deaths per 100,000 population decreased. Americas had the highest number of newly cumulative total deaths, Europe had the highest cumulative total deaths per 100,000 population. The Western Pacific had the lowest number of newly cumulative total deaths and cumulative total deaths per 100,000 population. The trend line shows that until July 23, 2021, the number of newly



**Fig. 4.** Depicts the number of newly reported cases and deaths in the last 24 hours until July 23, 2021. The trend lines showed an increase and decrease of the newly reported cases and deaths, respectively in the last 24 hours.



**Fig. 5.** The number of newly cumulative total deaths and cumulative total deaths per 100000 population until July 23, 2021. The trend lines showed a decrease of newly cumulative total deaths and cumulative total deaths per 100000 population.



**Fig. 6.** The number of newly cumulative total deaths and cumulative total deaths per 100,000 population in the last seven days until July 23, 2021. The trend line shows that the number of newly cumulative total deaths and cumulative total deaths per 100,000 population in the last seven days until July 23, 2021. The trend lines showed a decrease of newly cumulative total deaths and cumulative total deaths per 100000 population in the last seven days.

cumulative total deaths and cumulative total deaths per 100,000 population decreased in the last seven days. Americas had the higher number of newly cumulative total deaths and the highest cumulative total death per 100,000 population in the last seven days. Until July 23, 2021, Western Pacific had the lowest number of newly cumulative total deaths, but Eastern Mediterranean had the lowest cumulative total deaths per 100,000 population in the last seven days (Fig. 6). Furthermore, the trend line shows that until July 23, 2021, the number of newly cumulative total confirmed and deaths cases decreased. Although Americas had the higher number of newly cumulative total confirmed and death cases, Western Pacific had the lowest number of newly cumulative total confirmed and death cases until July 23, 2021 (Fig. 7).

### Immunology of COVID-19

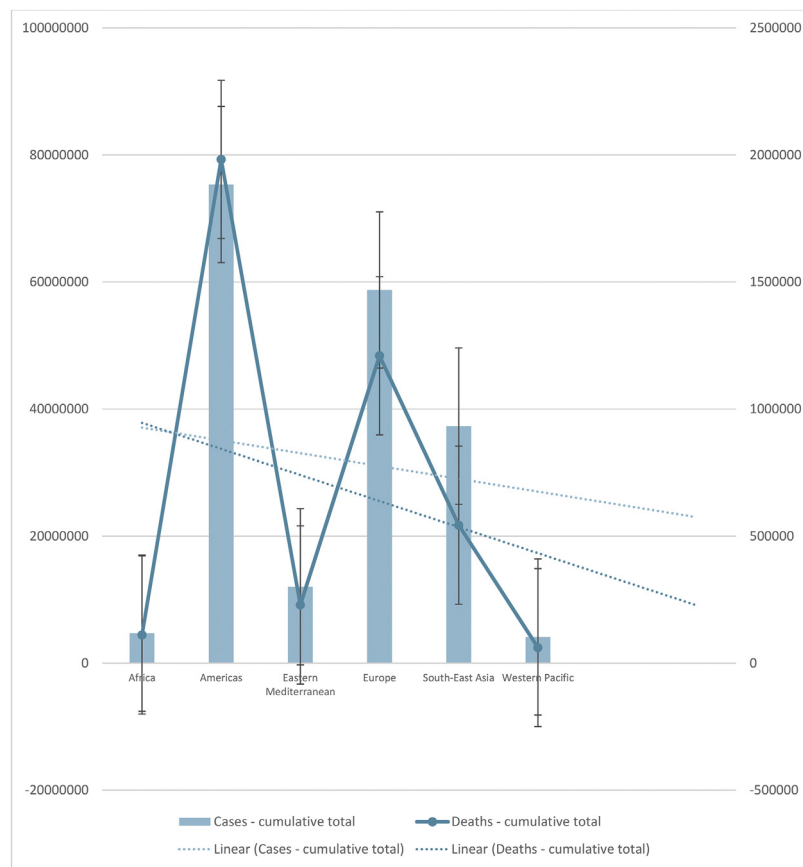
Most infected people (more than 80%) will develop mild to moderate illness without symptoms and recover without hospitalization, but less than 20% of infected patients have severe symptoms and are critically ill [20,21]. Presently, there is incomplete evidence on host factors affecting individual outcomes in COVID-19. Fever, dry cough, and tiredness are the most common symptoms; less common symptoms include aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, skin rash, and discoloration fingers or toes [22,23].

The first line of immunological defense against COVID-19, as with SARS-CoV-2 infection, is the innate immune system. The

development of COVID-19 infection is thought to occur from a complex interplay between multiple pathophysiological mechanisms as with SARS-CoV-2, where the mechanisms regulate SARS-CoV-2 infection and contribute to specific tissue damage in organs [24]. There are various immunity pathways mediated during SARS-CoV-2 infection, which are related to innate immunity, adaptive immunity, and autoimmunity. Pathological findings in tissue samples of patients with COVID-19 provide valuable information about our understanding of pathophysiology and the development of evidence-based treatment regimens [25].

### Infection mechanisms and immune evasion

To find the escape mechanism of COVID-19 from the host's immune response, one may extrapolate knowledge of SARS-CoV counterparts and MERS-CoV. Remarkably, COVID-19 has almost 80% RNA sequence homology in common with SARS-CoV, and 50% with MERS-CoV [17], with COVID-19 demonstrating different genomic regions compared to SARS-CoV. The viral spike protein bonded to the host cell receptor is longer than other related coronaviruses, particularly SARS-CoV with about 30 amino acids [26]. Thus, similar immune evasion strategies may be used by all coronaviruses. Nevertheless, undiscovered mechanisms may also be employed by COVID-19 [27]. Both SARS-CoV and COVID-19 use the host cell receptor, angiotensin-converting enzyme 2 (ACE2), to start the infection [28]. The ACE2 is found on surfactant generating type 2 alveolar cells and on related cells in the airways, which serves as



**Fig. 7.** The number of newly cumulative total confirmed and deaths cases until July 23, 2021. The trend lines showed a decrease of newly cumulative total confirmed and deaths cases.

an entry for viruses into the body [29–31]. High ACE2 expression is also observed on the intestinal epithelium [32].

#### Expression of ACE2

The expression of ACE2 on cardiac and vascular endothelial cells may elucidate cardiovascular complications in patients [16]. It is not evident whether and how the SARS-CoV-2 can also infect immune cells containing monocytes/macrophages and T cells. On monocytes and macrophages, the expression of ACE2 is not ubiquitously observed, and for SARS-CoV-2 this may offer a mechanism of entry into immune cells. Immune complexes, including other receptors and/or phagocytosis of the virus, are also apparent [33–35]. The expression of type I interferon (T1IFN) and signals of downstream modification responses into an ‘anti-viral state’, consequently encourages infection control and pathogen clearance [36]. Initially, immune cells find a virus-related infection from pathogen-associated molecular patterns (PAMPs). Pattern recognition receptors (PRRs) are then activated and cause the activation of the immune cell. SARS-CoV, COVID-19, and MERS-CoV are among the RNAs viruses, which the endosomal RNA PRRs distinguish, including toll-like receptors 3 (TLR-3) and sensors of cytoplasmic RNA, namely retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) [37–39].

Pathogen clearance and recovery have emerged due to activation and priming of innate and adaptive immune responses. The suppression of these mechanisms by COVID-19 in some cases to escape recognition by the immune system is seen in more severe infections and worse prognosis [40–43].

To some extent, the novel coronaviruses may also discharge these mechanisms inducing T cell apoptosis [44,45]. Lymphocytes

may also become exhausted due to pro-inflammatory cytokine expression by native immune cells engaged in the lungs and trigger hyper-inflammation during a cytokine storm [46,47].

#### Hyper inflammation

In some cohort studies, the key results were associated with negative consequences in COVID-19, as in SARS or MERS, as hyper-inflammation with more severe disease was suggested. Among 99 patients infected by COVID-19, the report showed the typical symptoms with percentages of 38, 35, and 52 related to neutrophilia, lymphopenia, and increased systemic inflammatory proteins of IL-6 CRP, respectively [48]. A study involving 41 individuals with severe disease terminating in an intensive care unit (ICU) admission or death presented with interconnected neutrophilia and lymphopenia [20]. In another study, substantial leukopenia (11.8%), lymphopenia (77.6%), thrombopenia (41.2%), anemia (48.2%), hypofibrinogenemia (22.4%), and hypo-albuminemia (78.8%) was reported among 85 cases of death from COVID-19 [49]. These observations agree with the results of severe conditions of MERS or lethal cases of SARS in which the presence of neutrophils and macrophages were increased in the airways [49,50]. Other studies of severe clinical phenotypes and ICU dependency of patients have presented a link with higher levels of plasma from innate chemokines, definitely the pro-inflammatory cytokine TNF- $\alpha$ , chemokine (C-C motif) ligand 2 (CCL2), C-X-C motif chemokine 10 (CXCL10), monocyte chemoattractant protein 1 (MCP-1), interferon gamma-induced protein 10 (IP-10), and macrophage inflammatory protein (MIP)-1 A/CCL3 [51,52]. This is a condition previously described in SARS and MERS inflammation with poor consequences.

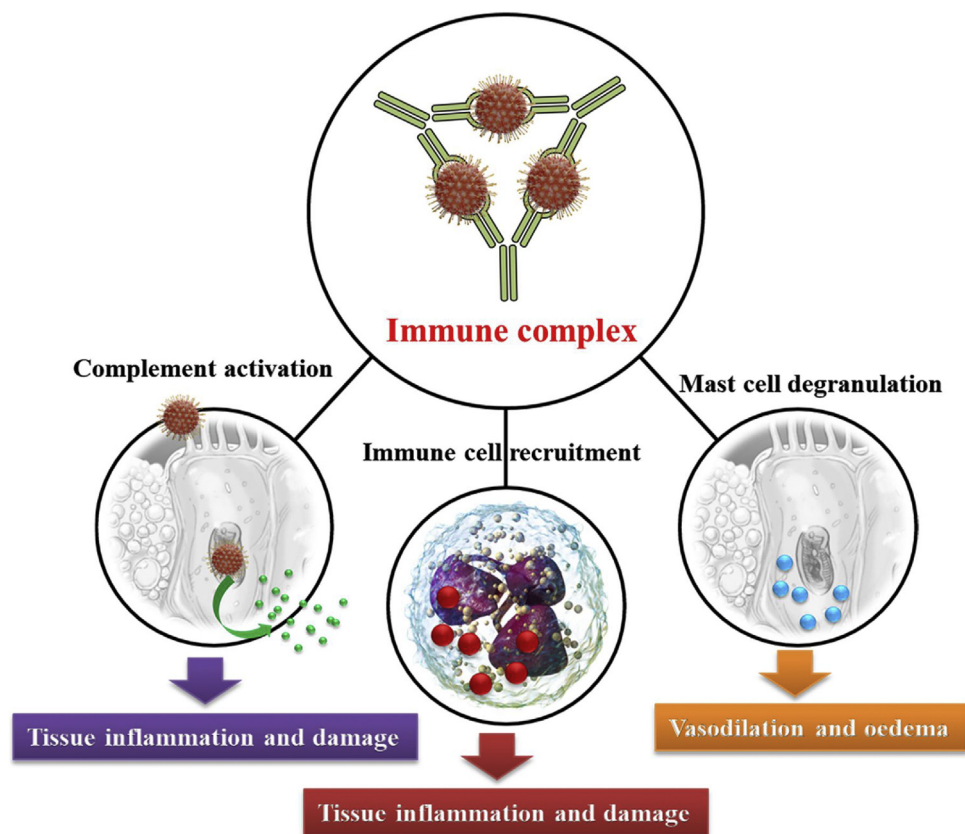


Fig. 8. A schematic illustration of inflammatory mechanisms in complex immune vasculitis.

Enhanced activation of the innate immune system contributes to morbidity and mortality in COVID-19, contradictory to immune evasion mechanisms, including expression activation of T11FN, IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . One probable description is that the endothelial induction, vascular cell damage, and cell death have resulted from replicating the COVID-19 virus. Cell deaths are due to inflammation, including necrosis or pyroptosis in pro-inflammatory cytokine expression, recruitment, and activation of immune cells [53]. It is proposed that uninfected immune cells recruited to the infection site show inflammatory responses of unwell and robust control, leading to damage of tissues and systemic inflammation [54].

The other probable explanation relates to the production of neutralizing antibodies against coronaviruses in the early stages of damaged organs. The phenomenon of antibody-dependent enhancement (ADE) increases damage throughout viral infections. It should be noted that the promotion of virus particle uptake is connected to immune system complexes in binding to Fc $\gamma$  receptors (Fc $\gamma$ R). Viral replication in immune cells and immune complexes are both mediated inflammatory responses in the damaged tissues of acute respiratory distress syndrome (ARDS) (Fig. 8) [46,55]. The histopathologic reports of tissues from COVID-19 patients showed the advanced features associated with immune complex-mediated vasculitis, including monocyte infiltration, thickening of blood vessels, and hemorrhage [56–58].

Generally, patients with severe symptoms of COVID-19 experience cytokine storm, lymphopenia, and often lymphatic tissue atrophy, specifically lymph nodes [59,60]. This cytokine storm corresponds to the reports of hemophagocytic lymphohistiocytosis (HLH), inspiring cell death and hypo-cellularity of lymphatic organs [61–63].

#### Effective host factors

The available data associated with age is insufficient, but children seemingly do not progress to severe indicators or difficulties associated with COVID-19. This is surprising as children are prone to viral infections comprising seasonal coronaviruses (75%) before four years. Nonetheless, increasing age leads to antibody decrease, especially over sixty years [64]. It can diminish the effective response of immune systems to COVID-19 in the elderly, as the reactivity is restricted to anti-seasonal coronavirus and anti-SARS antibodies with increased inflammation and complications.

The other age-dependent mechanism may be allied with live vaccinations (e.g., BCG). Vaccines protect the target antigen, which leads to non-specific heterologous effects due to the induction of innate immune mechanisms—individuals who receive BCG vaccinations as infants in response to *S. aureus* or *Candida* spp. produce increased pro-inflammatory IL-1 $\beta$  and TNF- $\alpha$  levels and reduced infection-related mortality [38].

Conversely, immune responses in a non-homogenous manner may also contribute to inflammation complications. Normally in adults, T cells do not have a memory of antigens they have not been exposed to, but cross-reactive memory T cells lead to slender responses by preferring clones with high affinity. The feature of immune senescence is due to the limited memory T cell repertoires, associated with disease progression and damage of T cell-mediated infections of hepatitis and virulent mononucleosis [65,66]. Lately it has been recommended that in children and young women, a higher expression of ACE2 is expected, which decreases with age. In contrast, the lowest expression is seen in chronic diseases such as diabetes and hypertension, in reverse correlation with risk for severe disease and negative effects [66].

### Immune modulating treatment

According to earlier SARS, MERS studies, and COVID-19 cohort studies, the determinants of old age, diabetes, metabolic syndrome, obesity, male, coronary heart disease, chronic obstructive pulmonary disease, and kidney disease are among the most reported risk factors [67]. It is noteworthy that in China and Italy, the suppression of the immune system was not acknowledged among these risk factors [68]. However, immune suppression and its associated functions may enhance virus spread.

Moreover, the infected cases receiving immune-modulating treatment may be prone to secondary infections due to the association of COVID-19 with lymphopenia. Some immune-modulating drugs can defend against viral infections. Unrestrained treatment termination of immune-modulating drugs may cause disease flares in autoimmune/inflammatory conditions or organ rejection. As evident, the risk for a viral infection is increased. Thus, international communities recommend treatment continuation in the absence of symptoms and modifications of current treatment regimens with clinical service monitoring [68,69].

### Conclusion

The outbreak of COVID-19 has caused concern around the world, and it is not evident whether and how SARS-CoV-2 can also infect immune cells. Different studies reported neutrophilia, lymphopenia, leukopenia, thrombopenia, anemia, hypofibrinogenemia, hypo-albuminemia, and increased systemic inflammatory proteins of IL-6 CRP. In severe conditions of MERS or lethal cases of SARS, neutrophils and macrophages are increased in the airways. The analysis of available data can help authorities in deciding how to control the virus worldwide. Thus, this study collected and analyzed data from articles and databases. Various researchers in different parts of the world analyze the available data to predict the prevalence of coronavirus in different countries; still, no analysis has been published that can predict the situation and future peaks. Following the review and analyzing of the published data on the WHO website and the data generated from the reported cases and trend lines, this study predicts that the number of confirmed cases (cumulative total) and deaths (cumulative total) caused due to coronavirus in different continents would decrease eventually. Intriguingly, although, the trend lines indicating that the number of confirmed cases (newly reported in the last 24 hours and last seven days) would increase, the number of deaths cases (newly reported in the last 24 hours and last seven days) will decrease in the long run. In the future, additional analyses based on the updated data and information are essential to confirm the prediction of this study.

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There was no conflict of interest.

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### References

- [1] Jiang S, Shi Z, Shu Y, Song J, Gao GF, Tan W, et al. A distinct name is needed for the new coronavirus. *Lancet (London, England)* 2020;395(10228):949.

- [2] Sheikhpour M. The current recommended drugs and strategies for the treatment of coronavirus disease (COVID-19). *Ther Clin Risk Manag* 2020;16:933.
- [3] COVID-19 Public Health Emergency of International Concern (PHEIC) Global research and innovation forumAccess date: July 23, 2021, URL: [https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-\(pheic\)-global-research-and-innovation-forum](https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-(pheic)-global-research-and-innovation-forum).
- [5] Saif LJ. Coronaviruses of domestic livestock and poultry: interspecies transmission, pathogenesis, and immunity. *Nidoviruses* 2007:279–98.
- [6] Drexler JF, Gloza-Rausch F, Glende J, Corman VM, Muth D, Goettsche M, et al. Genomic characterization of severe acute respiratory syndrome-related coronavirus in European bats and classification of coronaviruses based on partial RNA-dependent RNA polymerase gene sequences. *J Virol* 2010;84(21):11336–49.
- [7] Saif LJ. Coronaviruses of domestic livestock and poultry: interspecies transmission, pathogenesis, and immunity; 2007. p. 279–98.
- [8] Drexler JF, Drexler JF, Gloza-Rausch F, Glende J, Corman VM, Muth D, Goettsche M, et al. Genomic characterization of severe acute respiratory syndrome-related coronavirus in European bats and classification of coronaviruses based on partial RNA-dependent RNA polymerase gene sequences. *J Virol* 2010;84(21):11336–49.
- [9] Afelt A, Lacroix A, Zawadzka-Pawlewska U, Pokojski W, Buchy P, Frutos R. Distribution of bat-borne viruses and environment patterns. *Infect Genet Evol* 2018;58:181–91.
- [10] Mohan SV, Hemalatha M, Kopperi H, Ranjith I, Kumar AK. SARS-CoV-2 in environmental perspective: occurrence, persistence, surveillance, inactivation and challenges. *Chem Eng J* 2021;405:126893.
- [11] Fong SJ, Dey N, Chaki J. Artificial intelligence for coronavirus outbreak. Springer; 2020.
- [12] Sirdia Jr JA. Epidemiology and clinical features of COVID-19: a review of current literature. *J Clin Virol* 2020;104357.
- [13] Lakshmi Priyadarsini S, Suresh M. Factors influencing the epidemiological characteristics of pandemic COVID 19: a TISM approach. *Int J Healthc Manag* 2020;13(2):89–98.
- [14] Halaji M, Farahani A, Ranjbar R, Heiat M, Dehkordi FS. Emerging coronaviruses: first SARS, second MERS and third SARS-CoV-2: epidemiological updates of COVID-19. *Infez Med* 2020;28(suppl 1):6–17.
- [15] Surveillances V. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—china, 2020. *China CDC Weekly* 2020;2(8):113–22.
- [16] Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res* 2020;116(6):1097–100.
- [17] Binnicker MJ. Emergence of a novel coronavirus disease (COVID-19) and the importance of diagnostic testing: why partnership between clinical laboratories, public health agencies, and industry is essential to control the outbreak. *Clin Chem* 2020;66(5):664–6.
- [18] Zhang Y, Xu J, Li H, Cao B. A novel coronavirus (COVID-19) outbreak: a call for action. *Chest* 2020;157(4):e99–101.
- [19] Liu J, Xie W, Wang Y, Xiong Y, Chen S, Han J, et al. A comparative overview of COVID-19, MERS and SARS. *Int J Surg* 2020;81:1–8.
- [20] Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. *Nature* 2020;579(7798):265–9.
- [21] Kronbichler A, Effenberger M, Eisenhut M, Lee KH, Shin JI. Seven recommendations to rescue the patients and reduce the mortality from COVID-19 infection: an immunological point of view. *Autoimmun Rev* 2020:102570.
- [22] Mohammadbeigi M, Koshkoghi SA, Meskini M. An overview on wearing the face mask to avoid transmission of coronavirus disease 2019. *Rev Med Microbiol* 2020;31(4):221–33.
- [23] Mohammadi M, Meskini M, do Nascimento Pinto AL. 2019 Novel coronavirus (COVID-19) overview. *J Public Health (Bangkok)* 2019:1–9.
- [24] van Eijk LE, Binkhorst M, Bourgonje AR, Offringa AK, Mulder DJ, Bos EM, et al. COVID-19: immunopathology, pathophysiological mechanisms, and treatment options. *J Pathol* 2021.
- [25] Paland N, Pechkovsky A, Aswad M, Hamza H, Popov T, Shahar E, et al. The immunopathology of COVID-19 and the Cannabis paradigm. *Front Immunol* 2021;12:327.
- [26] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 2020;94(7).
- [27] Zhou H, Chen X, Hu T, Li J, Song H, Liu Y, et al. A novel bat coronavirus closely related to SARS-CoV-2 contains natural insertions at the S1/S2 cleavage site of the spike protein. *Curr Biol* 2020;30(11):2196–203, e3.
- [28] Zhu Y, Li J, Pang Z. Recent insights for the emerging COVID-19: drug discovery, therapeutic options and vaccine development, *Asian. J Pharm Sci* 2021;16(1):4–23.
- [29] Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med* 2020.
- [30] Lakkundi NV. Surfactant therapy and SP-D in managing COVID-19 ARDS—therapeutic role possible. *J PeerScientist* 2020;3(2):e1000029.
- [31] Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Internal Med* 2020;76:14–20.
- [32] Ziegler CG, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* 2020;181(5):1016–35, e19.

- [33] AbdelMassih AF, Ramzy D, Nathan L, Aziz S, Ashraf M, Youssef NH, et al. Possible molecular and paracrine involvement underlying the pathogenesis of COVID-19 cardiovascular complications. *Cardiovasc Endocrinol Metab* 2020;9(3):121.
- [34] Zhu H, Cheng P, Waliyany S, Chang A, Witteles RM, et al. Cardiovascular complications in patients with COVID-19: consequences of viral toxicities and host immune response. *Curr Cardiol Rep* 2020;22(5):1–9.
- [35] Guo J, Wei X, Li Q, Li L, Yang Z, Shi Y, et al. Single-cell RNA analysis on ACE2 expression provides insights into SARS-CoV-2 potential entry into the bloodstream and heart injury. *J Cell Physiol* 2020;235(12):9884–94.
- [36] Hosking MP, Flynn CT, Whitton JL. Type 1 IFN signaling is dispensable during secondary viral infection. *PLoS Pathog* 2016;12(8):e1005861.
- [37] Hedrich CM. COVID-19—considerations for the paediatric rheumatologist. *Clin Immunol* 2020;108420.
- [38] Felsenstein S, Hedrich CM. SARS-CoV-2 infections in children and young people. *Clin Immunol* 2020;108588.
- [39] Eswaran N, Krishna S. Coronavirus disease 2019 (COVID-19): pathogenesis, immune responses, and treatment options. *Asian J Res Infect Dis* 2020:37–54.
- [40] Thevarajan I, Nguyen TH, Koutsakos M, Druce J, Caly L, van de Sandt CE, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nat Med* 2020;26(4):453–5.
- [41] Mazzoni A, Salvati L, Maggi L, Capone M, Vanni A, Spinicci M, et al. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. *J Clin Invest* 2020;130(9).
- [42] Melenotte C, Silvin A, Goubet A-G, Lahmar I, Dubuisson A, Zumla A, et al. Immune responses during COVID-19 infection. *Oncoimmunology* 2020;9(1):1807836.
- [43] Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. *Nat Rev Immunol* 2020;20(6):339–41.
- [44] Wyllie AH. Apoptosis: an overview. *Br Med Bull* 1997;53(3):451–65.
- [45] Aghagholi G, Marin BG, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological involvement in COVID-19 and potential mechanisms: a review. *Neurocrit Care* 2020:1–10.
- [46] Asrani P, Hassan MI. SARS-CoV-2 mediated lung inflammatory responses in host: targeting the cytokine storm for therapeutic interventions. *Mol Cell Biochem* 2021;476(2):675–87.
- [47] Tang L, Yin Z, Hu Y, Mei H. Controlling cytokine storm is vital in COVID-19. *Front Immunol* 2020;11:3158.
- [48] Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci* 2020;57(6):389–99.
- [49] Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. *Am J Respir Crit Care Med* 2020;201(11):1372–9.
- [50] Dandekar AA, Perlman S. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat Rev Immunol* 2005;5(12):917–27.
- [51] Kelsven S, de la Fuente-Sandoval C, Achim CL, Reyes-Madrugal F, Mirzakhani H, Domingues I, et al. Immuno-inflammatory changes across phases of early psychosis: the impact of antipsychotic medication and stage of illness. *Schizophr Res* 2020;226:13–23.
- [52] Kawamoto D, Amado PPL, Albuquerque-Souza E, Bueno MR, Vale GC, Saraiva L, et al. Chemokines and cytokines profile in whole saliva of patients with periodontitis. *Cytokine* 2020;135:155197.
- [53] Wang X, Cao R, Zhang H, Liu J, Xu M, Hu H, et al. The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. *Cell Discov* 2020;6(1):1–5.
- [54] Martinez FO, Combes TW, Orsenigo F, Gordon S. Monocyte activation in systemic Covid-19 infection: assay and rationale. *EBioMedicine* 2020;59:102964.
- [55] Can A, Coskun H. The rationale of using mesenchymal stem cells in patients with COVID-19-related acute respiratory distress syndrome: what to expect. *Stem Cells Transl Med* 2020;9(11):1287–302.
- [56] Becker RC. COVID-19-associated vasculitis and vasculopathy. Springer; 2020.
- [57] Almasht SA. Vasculitis in COVID-19: a literature review. *J Vasc* 2020;6(1):1–5.
- [58] Prasad A. Looking beyond the cutaneous manifestations of covid 19, part 2: the pathology and Pathogenesis—a review. *Asian J Res Dermatol Sci* 2020:1–21.
- [59] Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol* 2020;39:2085–94.
- [60] Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. *Front Immunol* 2020;11:1708.
- [61] Soy M, Atagündüz P, Atagündüz I, Sucak GT. Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. *Rheumatol Int* 2020:1–12.
- [62] Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, et al. On the alert for cytokine storm: immunopathology in COVID-19. *Arthritis Rheumatol* 2020;72(7):1059–63.
- [63] Wei A, Ma H, Zhang L, Li Z, Zhang Q, Wang D, et al. Hemophagocytic lymphohistiocytosis resulting from a cytokine storm triggered by septicemia in a child with chronic granuloma disease: a case report and literature review. *BMC Pediatr* 2020;20(1):1–4.
- [64] Channappanavar R, Perlman S. Age-related susceptibility to coronavirus infections: role of impaired and dysregulated host immunity. *J Clin Invest* 2020. Oct 21.
- [65] Shaw ER, Su HC. The influence of immune immaturity on outcome after virus infections. *J Allergy Clin Immunol Pract* 2021;9(2):641–50.
- [66] Varadé J, Magadán S, González-Fernández Á. Human immunology and immunotherapy: main achievements and challenges. *Cell Mol Immunol* 2020:1–24.
- [67] Lai C-C, Liu YH, Wang C-Y, Wang Y-H, Hsueh S-C, Yen M-Y, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths. *J Microbiol Immunol Infect* 2020;53(3):404–12.
- [68] D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. *Liver Transplant* 2020;26(6):832–4.
- [69] Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open* 2020;3(4):e208857.
- [70] Ghosh S, Bornman C, Zafer MM. Antimicrobial Resistance Threats in the emerging COVID-19 pandemic: Where do we stand? *J Infect Public Health* 2021.
- [71] Alhourri A, Salloum A, Harfouch RM, Ghosh S. Antimicrobial Resistance Threats in the emerging COVID-19 pandemic: Where do we stand? *J Infect Public Health* 2021.