PANDEMIC IN INDIA OF COVID 19 AND COMMUNITY TRANSMISSION R. C. PATEL INSTITUTE OF PHARMACEUTICAL EDUCATION AND RESEARCH, SHIRPUR, MAHARASHTRA

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ABSTRACT

The mysterious coronavirus outbreak in the Chinese city Wuhan, now termed as COVID-19, and its fast spread to many other countries, endangers thousands of lives. Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While the majority of cases result in mild symptoms, some progress to pneumonia and multi-organ failure. People contract COVID-19 by touching a contaminated surface and then touching any orifice of body. The standard method of diagnosis is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab. Corona virus are large envelop virus of 80 to 200 nm in diameter. In addition to the three main structural proteins possessed by all coronaviruses, human coronaviruses (as well as HEV, MHV, MHV-JHM strain and BCV) possess a fourth protein, a haemagglutinin/esterase, termed HE, which also resides in the envelop. Coronavirus transmission can happen human-to-human as well as from infected animals such as dogs and cats. These symptoms may appear 2-14 days after exposure (based on the incubation period of MERS-CoV viruses). Coronavirus symptoms include those associated with common cold, such as running nose, headache, cough, fever, sore throat and shortness of breath. Chloroquine approved for emergency use by US FDA, Favipiravir, the first approved coronavirus drug in China, Gimsilumab, human monoclonal antibody, Remdesivir (GS-5734) by Gilead Sciences, Actemra (Tocilizumab), Chloroquine phosphate, AbbVie's HIV protease inhibitor, Lopinavir (200mg), Ritonavir (50mg), Darunavir, Cobicistat these are various drugs used against corona virus. Coronavirus

continues to spread across the globe, infecting tens of thousands of people in dozens of countries, making it a pandemic.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] The disease was first identified in 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally, resulting in the 2019–2020 coronavirus pandemic.[4,5] Common symptoms include fever, cough, and shortness of breath. Other symptoms may include muscle pain, sputum production, diarrhea, sore throat, abdominal pain, and loss of smell or taste.[1,6,7] While the majority of cases result in mild symptoms, some progress to more serious symptoms like pneumonia and multi-organ failure.[4,8] As of March 25, 2020, the overall rate of deaths per number of diagnosed cases is 4.5 percent; ranging from 0.2 percent to 15 percent according to age group and other health problems.[2]

The virus is mainly spread during close contact and via respiratory droplets produced when people cough or sneeze.[9,10] Respiratory droplets may be produced during breathing but the virus is not considered airborne.[10,11] People may also get infected by touching a contaminated surface and then their face.[9,10] It is most contagious when people are symptomatic, although spread is also possible even in the latent period of the virus.[10] The virus can live on surfaces up to 72 hours.[12] Latency period, that is the time from exposure to onset of symptoms is generally between two and fourteen days, with an average of five days.[13][14] The standard method of diagnosis is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab.[15] The infection can also be diagnosed from a combination of symptoms, risk factors and a chest CT scan showing features of pneumonia.[16,17]

Recommended measures to prevent infection include frequent hand washing, social distancing (maintaining physical distance from others, especially from those with symptoms), covering coughs and sneezes with a tissue or inner elbow, and keeping unwashed hands away from the face.[18,19] The use of masks is recommended by some national health authorities for those who suspect they have the virus and their caregivers, but not for the general public, although simple cloth masks may be used by those who desire them.[20,21] There is no vaccine or specific antiviral treatment for COVID-19. Management involves treatment of symptoms, supportive care, isolation, and experimental measures.[22]

The World Health Organization (WHO) declared the 2019–20 coronavirus outbreak a Public Health Emergency of International Concern (PHEIC) on 30 January 2020[23,24] and a pandemic on 11 March 2020.[5] Local transmission of the disease has been recorded in many countries across all six WHO regions.[25]

Structure of corona
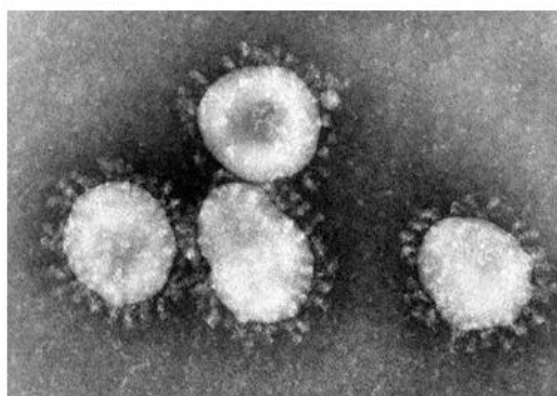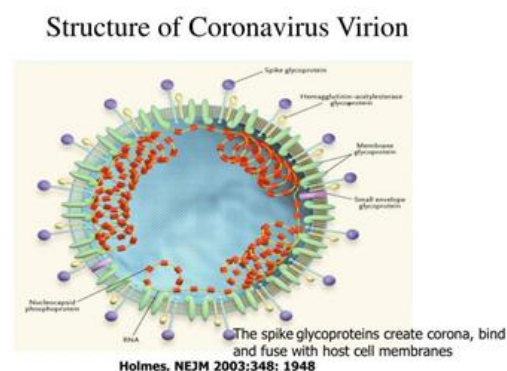

MICROSCOPIC IMAGE OF CORONA VIRUS   Fig.1

Structure and properties of the corona virus

Structure Coronaviruses are large enveloped viruses of 80 to 200 nm in diameter as measured by electron microscopy of negatively stained virions; the measured diameter of HCV-229E virions is significantly greater if the staining is by uranyl acetate than by potassium phosphotungstate.[29] They have a single-stranded RNA genome of positive polarity, and a buoyant density in sucrose of 1-18 g/ml. The characteristic morphological feature of all coronaviruses is the presence of a fringe of about 200 club-shaped projections of 10-20 nm in length that form the 'corona' (meaning crown) that gives the viruses their name. A general representation of a coronavirus is shown in Figure 1. The various structural components will now be discussed in detail; it should be noted that, despite the wealth of information on the physical components of human coronaviruses, the biological properties of these components have not been extensively investigated and are assumed to be similar to that shown for other coronaviruses; there is much evidence, however, to suggest that this assumption is reasonable. For a detailed review (and references) of the organisation and replication of coronaviruses the reader is referred elsewhere.[30] Human coronaviruses have been noted to have only one type of surface projection, these peplomers are 20 nm long and about 7nm wide at the tip. They are formed by a glycoprotein (termed S) of M, 160,000 - 200,000. It is

thought to be a dimer of two dissimilar proteins, which form tetramers to produce the surface peplomer or spike.

The spike can be removed from the rest of the virion by digestion with bromelain, and can then be separated into the district proteins of the dimers by digestion with trypsin. The predicted amino acid sequence of the surface protein from several strains of coronavirus is now available and the general structure seems to be of an N-terminal signal sequence, a membrane-spanning domain, and a C- terminal hydrophilic sequence; there are also a large number of glycosylation sites which in MHV have glucose amine and fructose residues. Mainly on the basis of experiments using specific monoclonal antibodies it is thought that the surface protein is responsible for the binding of the virus to cell surface receptors (and haemadsorption), inducing neutralising antibody, eliciting cell-mediated cytotoxicity, inducing cell fusion and the pH-dependent thermolability of coronaviruses. The most abundant protein is the membrane protein (designated M), which is present in approximately twice the amount of the nucleocapsid protein, 16 times the amount of the peplomeric protein, and over 30 times the amount of the HE protein. The M protein is really a set of four proteins (or complexes) of approximate molecular weight, 20000, 24000, 27000 and 40000 in human coronaviruses. The resultant protein size depends on the degree of glycosylation and on whether a dimer is formed. It is mainly embedded in the viral envelope but about 10% of the N-terminus end protrudes from the surface, and the C-terminus protrudes interiorly. There are differences in the composition of this protein in the two main groups of human coronaviruses, as exemplified[31] by the aggregation of HCV-OC43 M protein on heating in sodiumdodecyl sulphate, but not that of HCV- 229E. The M protein is essential for viral budding, forms the viral envelope and interacts with the nucleocapsid, possibly anchoring the genome to the viral envelope. The nucleocapsid protein (designated N) of molecular weight, 47000 - 55000 is nonglycosylated and basic, though it has an acidic C-terminus. Analysis of all the nonhuman mammalian coronaviruses so far has shown that it is also serine-rich. Its main role is to encapsulate the RNA genome, but evidence from studies with MHV, in which N-specific antiserum was added to an *in vitro* replication system, has shown that it may be important in RNA replication; in particular, the synthesis of genome-length RNA.

In addition to the three main structural proteins possessed by all coronaviruses, human coronaviruses (as well as HEV, MHV, MHV-JHM strain and BCV) possess a fourth protein, a hemagglutinin/esterase, termed HE, which also resides in the envelope. It is glycosylated,

has a molecular weight of 63000, exists as a dimer linked by a disulphide bridge and seems to be responsible for hemagglutination in the case of HCV-OC43. It may also play a role in binding to cell surfaces, and in BCV has been shown to have acetylesterase receptor destroying activity. Several minor proteins have been described in human coronaviruses, but no role has been ascribed to them, and indeed, it is now thought that some, if not all, of these polypeptides found in gel analyses are subcomponents of the four major proteins. The genome of coronaviruses is a single strand of positive-sense RNA that in human coronaviruses appears to have a molecular weight of about 6 million when run with known molecular weight markers in gels; this may be an underestimate as it was for IBV which has now been sequenced and found to be 27 kilobase (kb) long, the largest viral RNA virus genome determined so far. It has a polyadenylated tail at the 3' end, and is infectious. It is heat labile, tending to fragment above 60°C. It is intimately associated with the nucleoprotein and can be seen under the electron microscope to be in a helical arrangement. Nucleotide sequence data are now available from over 6.7kb of the 3' end of the virus of HCV-229E which covers the open reading frames for mRNAs 2 (translated to produce S protein)[28] 3, 4, 6(M protein)[32,33] and 7 (N protein)[26,27] mRNA 4 has two open reading frames which potentially code for a 44 amino acid polypeptide of molecular weight, 4600 and a polypeptide of 83 amino acids (MW 9000) which is basic and leucine-rich.[34,35] The nucleotide sequences of the genes coding for the membrane, surface and haemagglutinylesterase proteins of HCV-OC43 are also now available and predict structures similar to those of related animal viruses.

The envelope of coronaviruses is thought to be derived from the internal membranes from which they bud (see replication strategy), and indeed experiments with TGEV have shown that the lipid composition of the virus is dependent on the cells it is grown in, and accurately reflects the lipid composition of these cells. There may be a biological advantage for viruses budding from internal membranes over those budding from plasma membranes, as the former membranes are less susceptible to solubilisation by bile salts and other detergents, thus conferring a survival advantage in the intestinal tracts of hosts. Other host derived components have been described for various coronaviruses, including cellular proteoglycans, but it is difficult to ascertain whether these are artifacts of the virus purification procedures.

Clinical features

Coronavirus transmission

COVID-19 is a beta coronavirus that has origin in bats, according to the Centers for Disease Control and Prevention (CDC). It is believed to have transmitted from animals and reptiles such as snakes, coronaviruses cause respiratory issues such as upper respiratory tract illnesses and lower respiratory illnesses such as pneumonia and bronchitis. Coronavirus transmission can happen human-to-human as well as from infected animals such as dogs and cats.

It is generally assumed that common cold viruses are transmitted by aerosols but this is disputable. An editorial in the Lancet in 1988 summaries the research into the two alternative hypotheses, namely, aerosol spread and direct transmission by fingers or fomites. It is possible to spread colds from infected volunteers to uninfected volunteers, though often with some difficulty, with the two groups separated either temporally or spatially; HCV-229E has also been shown to survive airborne for days at medium to high humidity. It has, however, also been shown that rhinoviruses could survive on hands and inanimate objects and thus allow transmission in that manner. The likelihood is that both routes may occur but, in vivo, transmission by aerosol is the common one.

Common colds Coronaviruses are thought to cause up to 30% of all colds. The peak incidence seems to be during the period from the end of autumn to the beginning of spring when rhinovirus colds, which predominate at other times of the year, are relatively infrequent. Prevalence of antibodies to one or other human coronavirus is very high, being 6 - 37% in infants less than I year of age, 54 - 80% in the 1 - 5 year age group, and 100% in those over 5 years of age; this figure drops slightly with adult population. Out breaks of coronavirus infection seem to show 2-3 year cycles, HCV-229E epidemics alternating with HCV-OC43 infection. After an incubation period of 2-4 days, an illness comprising general malaise, headache, profuse rhinorrhoea, nasal blockage and sneezing is produced. HCV-OC43 infection also tends to result in a cough and pharyngeal hyperaemia, this being a less common feature of HCV- 229E infection. Both can produce a fever, enlargement of the cervical glands, and gastrointestinal symptoms (abdominal pain or diarrhoea). This illness lasts from 3 to 18 days, with a mean duration of 7 days. In serological surveys and volunteer studies, 30% of infected individuals remain asymptomatic.

Lower respiratory tract infection Coronaviruses have also been associated with lower respiratory tract illness in sero-epidemiological though it should be noted that in one early

study there was a higher incidence of coronavirus infections in the control group than in the diseased. The peak incidence of HCV- 229E lower respiratory tract infection seems to be in preschool children, and is rare in infants and adults; it presents as croup, bronchitis or pneumonia. In a 3-year study in the USA coronaviruses were found to be the third most common cause of bronchiolitis and pneumonia, after para-influenza 3 and respiratory syncytial virus, in 417 children under the age of 18 months. HCV-OC43 is more likely than HCV-229E to cause lower respiratory tract infection in adults. Asthmatic children and the elderly seem to be at particular risk of lower respiratory tract infection, and recent data would suggest that coronaviruses are the second or third most frequently identified agent responsible for precipitating acute wheezing in asthmatic children (unpublished data).

Symptoms

Reported illnesses have ranged from mild symptoms to severe illness and death for confirmed coronavirus disease 2019 (COVID-19) cases. These symptoms may appear 2-14 days after exposure (based on the incubation period of MERS-CoV viruses). Symptoms include fever, cough, shortness of breath. If emergency warning signs for COVID-19 are developed get medical attention immediately. Emergency warning signs include: troubling breathing, persistent pain or pressure in the chest, new confusion or inability to arouse, bluish lips or face, trouble.

Diagnosis

If an individual develop symptoms of coronavirus disease 2019 (COVID-19) and has been exposed to the virus, a medical checkup is necessary. If the individual has traveled to any areas, then he/she should inform the physician, considering the ongoing community spread of COVID-19 according to CDC and WHO. Also the individual must let the doctor know if you've had close contact with anyone who has been diagnosed with COVID-19. The doctor may determine whether to conduct tests for COVID-19 based on signs and symptoms. To decide whether to conduct tests for COVID-19, he or she may also consider whether the patient have had close contact with someone diagnosed with COVID-19 or traveled to or lived in any areas with ongoing community spread of COVID-19 in the last 14 days. To test for COVID-19, your doctor may take samples, including a sample of saliva (sputum), a nasal swab and a throat swab, to send to a lab for testing.[38]

Prevention

- There is currently no vaccine to prevent coronavirus disease 2019 (COVID-19).

- The best way to prevent illness is to avoid being exposed to this virus.

- The virus is thought to spread mainly from person-to-person.

- Between people who are in close contact with one another (within about 6 feet).

- Through respiratory droplets produced when an infected person coughs or sneezes.

- These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs.

- Following precautions must be taken to prevent risk of infection.

- Washing hands often with soap and water for at least 20 seconds especially after having been in a public place, or after blowing nose, coughing, or sneezing.

- If soap and water are not readily available, a hand sanitizer that contains at least 60% alcohol can also be used, the hands should be rubbed together until they feel dry.

- Avoid touching eyes, nose, and mouth with unwashed hands.[39]

- Avoid close contact with people who are sick.

- Put distance between yourself and other people if COVID-19 is spreading in your community. This is especially important for people who are at higher risk of getting very sick.

- Stay home if sick, except to get medical care.

- Covering mouth and nose with a tissue while coughing or sneezing or use of inside of the elbow.

- Throwing used tissues in the trash.

- If sick: a facemask should be used when around other people (e.g., sharing a room or vehicle) and before entering a healthcare provider's office. If wearing a facemask is troubling (for example, it causes trouble breathing), then steps to cover your coughs and sneezes must be taken, and people who are caretakers should wear a facemask if they enter the patient's room.

- If not sick: a facemask is not needed unless you are caring for someone who is sick (and they are not able to wear a facemask). Facemasks may be in short supply and they should be saved for caregivers.[39]

- Clean and disinfect frequently touched surfaces daily. This includes tables, doorknobs, light switches, countertops, handles, desks, phones, keyboards, toilets, faucets, and sinks.

- If surfaces are dirty, clean them: Use detergent or soap and water prior to disinfection. Most common EPA-registered household disinfectants will work. Use disinfectants appropriate for the surface.

Options include

Diluting household bleach. (5 tablespoon bleach per gallon of water).

Medication

The pandemic has catalysed the development of novel coronavirus vaccines across the biotech industry, both by pharmaceutical companies and research organisations such as the National Institutes of Health (NIH), US. The first COVID-19 vaccine in China is expected to be ready for clinical trials by the end of April, Inovio Pharmaceuticals plans to begin clinical trials on a coronavirus vaccine in April 2020. Health officials from WHO have noted that Gilead's remdesivir has demonstrated efficacy in treating the coronavirus infection.[40]

The US Food and Drug Administration (FDA) approved limited emergency use for chloroquine and hydroxychloroquine as a treatment for COVID-19. Favilavir, the first approved coronavirus drug in China**.** Favilavir, an anti-viral drug, as a treatment for coronavirus. The drug has reportedly shown efficacy in treating the disease with minimal side effects.

Novel coronavirus vaccines

Fusogenix DNA vaccine by entos pharmaceuticals

Fusogenix DNA vaccine developed using the Fusogenix drug delivery platform to prevent COVID-19 infections.

ChAdOx1 nCoV-19 by university of oxford

An adenovirus vaccine vector.

Gimsilumab, human monoclonal antibody.

The drug targets granulocyte-macrophage colony stimulating factor (GM-CSF), which is a pro-inflammatory cytokine found in high levels in the serum of COVID-19 patients.

AdCOVID by Altimmune

Intranasal vaccine for COVID-19 named AdCOVID.

TJM2 by I-Mab Biopharma

TJM2, a neutralising antibody, as a treatment for cytokine storm in patients suffering from a severe case of coronavirus infection. The company's research activities are being partly funded by the Canadian Institutes for Health Research (CIHR).

AT-100 by Airway Therapeutics

Novel human recombinant protein named AT-100 (rhSP-D) as a treatment for coronavirus.

TZLS-501 by Tiziana Life Sciences

Tiziana Life Sciences is developing its monoclonal antibody named TZLS-501 for the treatment of COVID-19. TZLS-501 is a human anti-interleukin-6 receptor (IL-6R), which helps in preventing lung damage and elevated levels of IL-6.

OYA1 by OyaGen

OyaGen's OYA1 has shown strong antiviral efficacy against coronavirus in laboratory essays. It was found to be more effective than chlorpromazine HCl in inhibiting SARS-CoV-2 from replicating in cell culture.

Altimmune's intranasal coronavirus vaccine

An intranasal Covid-19 vaccine is being developed by US-based clinical-stage biopharmaceutical company, Altimmune.

NP-120 (Ifenprodil) by Algernon Pharmaceuticals

Algernon Pharmaceuticals has announced that it is exploring its NP-120 (Ifenprodil) as a potential treatment COVID-19.

APN01 by University of British Columbia and APEIRON Biologics

A drug candidate developed by APEIRON Biologics named APN01

mRNA-1273 vaccine by Moderna and Vaccine Research Center

Moderna and the Vaccine Research Center, a unit of the National Institute of Allergy and Infectious Diseases (NIAID), have collaborated to develop a vaccine for coronavirus.

TNX-1800 by Tonix Pharmaceuticals

To develop a vaccine for coronavirus named TNX-1800.

CytoDyn-leronlimab

CytoDyn is examining leronlimab (PRO 140), a CCR5 antagonist, as a potential coronavirus drug.

MERS CoV vaccines for coronavirus

Coronavirus drugs

The novel coronavirus drugs in various stages of development globally are listed below.

Remdesivir (GS-5734) by Gilead Sciences

Actemra by Roche to treat coronavirus-related complications

The antiviral drug

Biocryst Pharma's Galidesivir, a potential antiviral for coronavirus treatment Galidesivir (BCX4430) has shown broad-spectrum activity against a wide range of pathogens including coronavirus. Chloroquine phosphate has shown efficacy in treating symptoms of the disease,

Takeda pharmaceutical company

The anti-SARS-CoV-2 polyclonal hyperimmune globulin (H-IG) therapy will be designed to treat high-risk patients.

Heat biologics

Heat Biologics has announced plans to develop a vaccine to treat or prevent coronavirus infection using its proprietary gp96 vaccine platform.

Coronavirus vaccine by ImmunoPrecise Antibodies

The company has updated its research efforts and noted that it will be using the PolyTope mAb Therapy™ and EVQLV's artificial intelligence platforms develop a COVID-19 therapy.

Serum Institute of India

Serum Institute of India (SII) is collaborating with Codagenix, a US-based biopharmaceutical company, to develop a cure for coronavirus using a vaccine strain similar to the original virus. The vaccine is currently in the pre-clinical testing phase, while human trials are expected to commence in the next six months. SII is expected to launch the vaccine in the market by early 2022.

HIV drugs for coronavirus treatment

Abbvie's HIV protease inhibitor, lopinavir is being studied along with ritonavir for the treatment of MERS and SARS coronaviruses.

The combination is listed in the WHO list of essential medicines. Lopinavir is believed to act on the intracellular processes of coronavirus replication and demonstrated reduced mortality in the non-human primates (NHP) model of the MERS.

Lopinavir/ritonavir in combination with ribavirin showed reduced fatality rate and milder disease course during an open clinical trial in patients in the 2003 SARS outbreak.

Cipla is also reportedly planning to repurpose its HIV drug LOPIMUNE, which is a combination of protease inhibitors Lopinavir and Ritonavir, for the treatment of coronavirus.

A licensed generic of Kaletra[®], LOPIMUNE is currently available in packs of 60 tablets each, containing 200mg of Lopinavir and 50mg of Ritonavir.

Janssen Pharmaceutical Companies, a subsidiary of Johnson & Johnson, donated its PREZCOBIX[®] HIV medication (darunavir/cobicistat) for use in research activities aimed at finding a treatment for COVID-19.

ritonavir marketed by Janssen. Anecdotal reports suggest darunavir as potentially having antiviral activity against COVID-19. It is, however, currently approved only for use with a boosting agent, and in combination with other antiretrovirals, for the treatment of HIV-1.

Outbreak of corona virus

As coronavirus continues to spread across the globe, tens of thousands of people have been infected in dozens of countries. The disease, known as COVID-19, originated in China, which has the highest number of confirmed cases to date, but it is now impacting every continent except Antarctica.

The spread of the deadly virus can be tracked with the help of maps and charts below, which will update daily with the latest data from the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and other sources compiled by Johns Hopkins University.[41]

Total global confirmed cases

801,400

Total deaths

38,743

Total recovered

172,657

Last updated: 3/31/20 at 5:13 PM

SOURCE Johns Hopkins University; WHO; CDC; USA TODAY
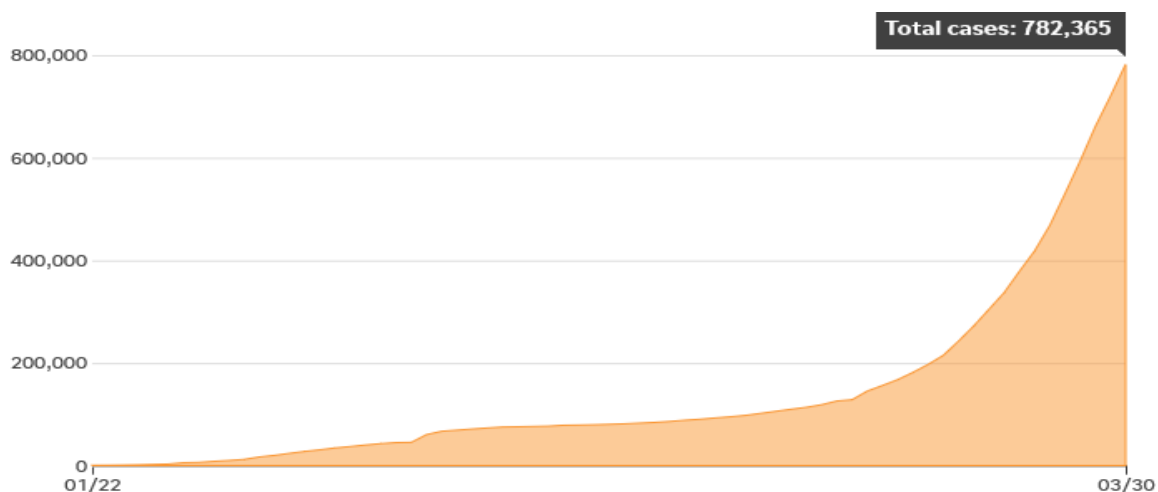
Last updated: 3/30/20

SOURCE Johns Hopkins University; WHO; CDC; USA TODAY

Coronavirus cases in Italy, Iran, Spain and around the world
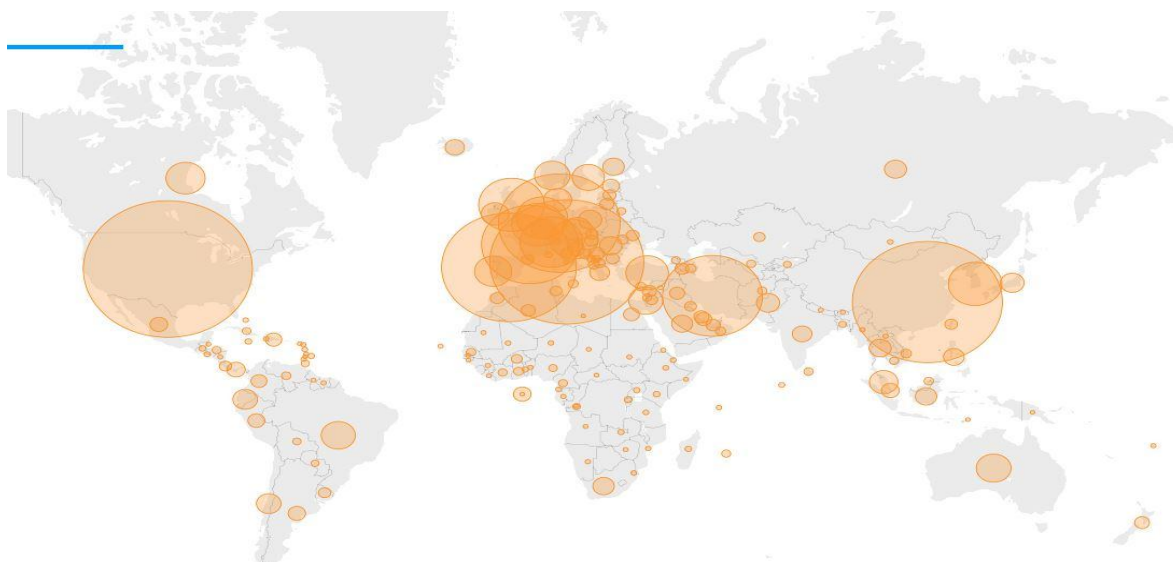
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SOURCE Johns Hopkins University; WHO; CDC; USA TODAY

US

Italy 161,807

Spain

101,739

87,956

China 82,198

Germany 66,885

France 45,170

Last updated: 3/31/20 at 1:44 PM

Total cases, deaths, and recoveries by country

	Country	Total cases	Recovered	Deaths
1	US	164,610	5,945	3,170
2	Italy	101,739	14,620	11,591
3	Spain	94,417	19,259	8,189
4	China	82,276	76,204	3,309
5	Germany	67,051	15,824	651
6	France	45,171	7,964	3,030
7	Iran	44,605	14,656	2,898
8	United Kingdom	22,465	179	1,412
9	Switzerland	16,176	1,823	373
10	Belgium	12,775	1,696	705

11	Netherlands	11,817	253	865
12	Turkey	10,827	162	168
13	Austria	9,876	1,095	128
14	Korea, South	9,786	5,408	162
15	Canada	7,448	1,020	89
16	Portugal	7,443	43	140
17	Israel	4,831	163	17
18	Brazil	4,661	127	165
19	Australia	4,559	358	18
20	Norway	4,495	13	34
21	Sweden	4,028	16	146
22	Czechia	3,002	25	25
23	Denmark	2,994	77	90
24	Ireland	2,910	5	54
25	Malaysia	2,766	537	43
26	Chile	2,449	156	8
27	Russia	2,337	121	17
28	Romania	2,245	220	69
29	Poland	2,132	7	31
30	Philippines	2,084	49	88

31	Luxembourg	1,988	80	22
32	Ecuador	1,966	54	62
33	Japan	1,953	424	56
34	Pakistan	1,865	76	25
35	Thailand	1,651	342	10
36	Indonesia	1,528	81	136
37	Saudi Arabia	1,453	115	8
38	Finland	1,418	10	13
39	South Africa	1,326	31	3
40	India	1,251	102	32
41	Greece	1,212	52	46
42	Mexico	1,094	35	28
43	Iceland	1,086	157	2
44	Panama	1,075	9	27
45	Argentina	966	228	24
46	Peru	950	53	24
47	Dominican Republic	901	4	42
48	Singapore	879	228	3
49	Slovenia	802	10	15
50	Colombia	798	15	14

51	Croatia	790	67	6
52	Serbia	785	0	16
53	Estonia	745	26	4
54	Diamond Princess	712	603	10
55	Qatar	693	51	1
56	Egypt	656	150	41
57	New Zealand	647	74	1
58	Iraq	630	152	46
59	United Arab Emirates	611	61	5
60	Algeria	584	37	35
61	Morocco	574	15	33
62	Ukraine	549	8	13
63	Lithuania	533	7	7
64	Armenia	532	30	3
65	Bahrain	515	295	4
66	Hungary	492	37	16
67	Lebanon	463	35	12
68	Bosnia and Herzegovina	411	17	10
69	Latvia	398	1	0
70	Bulgaria	379	17	8

71	Andorra	370	10	8
72	Slovakia	363	7	0
73	Tunisia	362	3	9
74	Kazakhstan	336	22	2
75	Costa Rica	330	4	2
76	Taiwan*	322	39	5
77	Uruguay	320	25	1
78	Moldova	298	18	2
79	Kuwait	289	73	0
80	North Macedonia	285	12	7
81	Azerbaijan	273	26	4
82	Jordan	268	26	5
83	Burkina Faso	246	31	12
84	Albania	243	52	13
85	Cyprus	230	22	7
86	San Marino	230	13	25
87	Vietnam	207	57	0
88	Cameroon	193	5	6
89	Oman	192	34	0
90	Senegal	175	40	0

91	Afghanistan	174	5	4
92	Cuba	170	4	4
93	Malta	169	2	0
94	Cote d'Ivoire	168	6	1
95	Uzbekistan	158	7	2
96	Belarus	152	47	0
97	Ghana	152	2	5
98	Mauritius	143	0	3
99	Honduras	141	3	7
100	Nigeria	135	8	2
101	Venezuela	135	39	3
102	Sri Lanka	132	16	2
103	Brunei	129	45	1
104	West Bank and Gaza	117	18	1
105	Georgia	110	21	0
106	Cambodia	109	23	0
107	Bolivia	107	0	6
108	Kyrgyzstan	107	3	0
109	Kosovo	106	1	1
110	Montenegro	105	0	1

111	Congo (Kinshasa)	98	2	8
112	Trinidad and Tobago	85	1	3
113	Rwanda	70	0	0
114	Paraguay	65	1	3
115	Liechtenstein	64	0	0
116	Bangladesh	51	25	5
117	Kenya	50	1	1
118	Monaco	49	1	1
119	Madagascar	46	0	0
120	Guatemala	36	10	1
121	Jamaica	36	2	1
122	Zambia	35	0	0
123	Barbados	34	0	0
124	Uganda	33	0	0
125	El Salvador	32	0	0
126	Togo	30	1	1
127	Niger	27	0	3
128	Ethiopia	25	2	0
129	Mali	25	0	2
130	Guinea	22	0	0

131	Congo (Brazzaville)	19	0	0
132	Tanzania	19	1	1
133	Djibouti	18	0	0
134	Maldives	18	13	0
135	Gabon	16	0	1
136	Eritrea	15	0	0
137	Haiti	15	1	0
138	Bahamas	14	1	0
139	Burma	14	0	1
140	Dominica	12	0	0
141	Equatorial Guinea	12	0	0
142	Mongolia	12	2	0
143	Namibia	11	2	0
144	Seychelles	10	0	0
145	Syria	10	0	2
146	Eswatini	9	0	0
147	Grenada	9	0	0
148	Laos	9	0	0
149	Saint Lucia	9	1	0
150	Guinea-Bissau	8	0	0

151	Guyana	8	0	1
152	Libya	8	0	0
153	Mozambique	8	0	0
154	Suriname	8	0	0
155	Zimbabwe	8	0	1
156	Angola	7	1	2
157	Antigua and Barbuda	7	0	0
158	Chad	7	0	0
159	Saint Kitts and Nevis	7	0	0
160	Sudan	7	0	2
161	Benin	6	1	0
162	Cabo Verde	6	0	1
163	Holy See	6	0	0
164	Mauritania	6	2	1
165	Fiji	5	0	0
166	Nepal	5	1	0
167	Bhutan	4	0	0
168	Gambia	4	0	1
169	Nicaragua	4	0	1
170	Belize	3	0	0

171	Botswana	3	0	0
172	Central African Republic	3	0	0
173	Liberia	3	0	0
174	Somalia	3	1	0
175	MS Zaandam	2	0	0
176	Papua New Guinea	1	0	0
177	Saint Vincent and the Grenadines	1	1	0
178	Timor-Leste	1	0	0

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