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COVID-19 pandemic dynamics

Nora Marie Ramm-Pettersen[1], Silja Lea[1], Christopher Truszkowski[1], Oda Henstein[1], Adriana Nudga[1], Simen Hagtvedt[1], Mohamed Abdel Latif[1], Håkon Hagtvedt[1], Ila Kela[1], Wilhelm Skjerven[1], Vasvi Sadhwani[1], Yaren Giray[1], Olivia Wicksell[1]

Introduction

The coronavirus disease, commonly referred to as COVID-19, is the result of an infection with the novel betacoronavirus which causes severe acute respiratory syndrome due to coronavirus 2 (SARS-CoV-2) [1]. The World Health Organization (WHO) became aware of this new virus on 31 December 2019 after a series of viral pneumonia cases reported from Wuhan in the People's Republic of China [2]. Following the primary reports of this novel betacoronavirus, now more commonly known as SARS-CoV-2, situation quickly developed into a global pandemic despite several efforts to control the initial spread of the virus. Current data suggest an incubation period of approximately 7 days [3]. SARS-CoV-2 primarily spreads through the respiratory tract, by droplets, respiratory secretions, and direct contact [4]. The clinical presentation of coronavirus disease may vary from mild illness to respiratory distress syndrome and death. When infected with SARS-CoV-2 the primary clinical picture presents with fever, cough and lethargy. In addition to these symptoms it has also been reported that some may experience a loss of taste and smell, a sore throat, headache and diarrhoea. The more serious symptoms reported following infection with SARS-CoV-2 are dyspnoea, and the development of acute respiratory distress syndrome, multi-organ dysfunction/failure and possibly death [4]. Several studies have shown that elderly and especially those with chronic diseases such as diabetes, cardiovascular disease, renal disease or lung disease are more likely to follow a more serious clinical presentation if infected.

Variants

All viruses, including SARS-CoV-2, have a tendency to mutate over time. Most mutations have little to no major impact on the characteristics of the virus, but some mutations may affect the virus properties. For example, the virus mutation could result in alterations of the spike proteins which are commonly used as a target for pharmaceutical therapies. Mutations could alter how easily the virus can spread, the disease severity or the efficacy of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures [5]. Since the first report of SARS-CoV-2 came in December of 2019, the virus has evolved and new variants of the SARS-CoV-2 virus have emerged. Mutations that have been within the spike protein have been of particular interest, as the spike protein

mediates the attachment of the virus to the host-cell surface and facilitates entry of the virus. And thus mutations in the spike protein have played an important role in the increased transmission of the virus, as well as changes in typical symptoms, and a decline in the vaccine protection. The United States Centers for Disease Control and Prevention (CDC) and WHO divide the emerging variants into two main classifications, namely variants of concern and variants of interest. To this date the SARS-CoV-2 variants that have been identified as variants of concern are the Alpha, Beta, Gamma, Delta and the newest Omicron variant. Variants of concern are variants that have been classified as having changes that to a significant degree has affected the public health significance. Therefore we have decided to focus on these variants rather than the variants of interest in this article.

Alpha

The Alpha variant, belonging to the B.1.1.7 lineage was reported in the UK in December 2020 [6]. The B.1.1.7 variant includes 23 mutations in the viral genome. Of these, eight mutations are in the spike protein. It was reported to be more transmissible than the previous COVID-19 variants, with transmission increasing by around 40-90% [7]. It has been identified that the alpha variant carried a more severe disease course, and that the risk of death was greater than with the previous variants.

Beta

The Beta variant, belonging to the B.1.351 lineage was detected in South Africa in late December 2020 [7]. The variant had 12 mutations within the spike protein, which contributed to increasing the viral transmission of the virus even further and reduced the effectiveness of the vaccines.

Gamma

The Gamma variant, belonging to the P.1 lineage, was reported in Brazil in December 2020. 10 mutations within the spike protein were recognized, and the Gamma variant was reported to have a higher resistance against the vaccines [6].

Delta

The Delta variant, belonging to the B.1.617.2 lineage, was identified in India in December 2020, and was responsible for one of the most deadly waves of COVID-19. The delta variant harboured 10 mutations in the spike protein, and was reported to be twice as contagious, as well as carrying a more severe course than the previous variants. The effectiveness of the vaccines decreased, but the coverage of severe illness was identified as being sufficient [6].

Omicron

The fifth and to this day the dominant variant of COVID–19, namely the Omicron variant, belonging to the B.1.1.529 lineage was first identified in South Africa in November 2021. The variant quickly spread and over 30 changes in the spike protein were recognized. The variant carried a significant increase in viral infectivity, as well as a decrease in the protection of the vaccines, but according to reports and research to this date the impact on the severity of the virus is reduced. The vaccines are as of now reported to protect well against severe illness, hospitalizations and death. More data are needed to fully understand the severity and associated mortality of the Omicron variant [6].

COVID-19 clinical course

Severity of disease (and its determinants). Individuals infected by the COVID-19 virus can experience a large range of clinical manifestations ranging from no symptoms to critical illness. The criteria are based on clinical trials and the status of a patient may change over time.

The initial clinical evaluation of a patient focuses on the following factors [8]:

- The date of onset of symptoms
- Risk factors (age>65 years, immuno-compromised state, obesity (with BMI >35), diabetes mellitus, chronic kidney disease)
- Treatment limiting organ dysfunction (hepatic, renal)
- Severity of disease
- Child or adolescent
- Vaccination status
- Virus variant (see the section on Variants, above)

Based on the aforementioned criteria, the disease is divided into: asymptomatic or presymptomatic infection, mild illness, moderate illness, severe illness and critical illness (Table 1) [9].

Studies have shown that COVID-19 affects certain population groups more than others. The known underlying medical conditions or risk factors that put one at a greater risk of COVID-19 include: asthma, cancer, cerebrovascular disease, chronic kidney disease, obesity or a weakened immune system [10]. While increasing age has demonstrated to be the strongest risk factor for COVID-19 outcomes, the severity increases as the number of underlying comorbidities increase in an individual [11]. Studies have shown that some disabilities may put a person at a higher risk of infection, and result in a worse outcome [12]. Adults with lifelong disabilities living in prisons, foster homes, long-term nursing homes, or assisted living may face a high risk of contracting the virus due to living in closer proximity to one another, and interacting with friends, staff, individuals, providers living outside of their accommodation [13]. Moreover, researchers have discovered an association between certain mental health conditions such as depression and schizophrenia spectrum disorders with increased risk of COVID-19 hospitalization and death [14]. Pregnant or postpartum women have a higher risk of severe illness, complications and death from COVID-19 compared to those who are not pregnant [15].

Table 1. COVID-19 severity with associated disease symptoms based on American College of Emergency Physicians COVID-19 Field Guide [9].

Severity	Indicators
Asymptomatic or presymptomatic infection	No symptoms
Mild illness	Fever, cough, sore throat, diarrhoea, loss of taste or smell but no dyspnoea; normal O_2 saturation and normal chest X ray
Moderate illness	Symptoms of mild disease plus evidence of lower respiratory tract infection (exam and/or imaging), O_2 saturation ≥94% on room air
Severe illness	Symptoms of moderate disease but O_2 saturation <94%, PaO_2/FiO_2 <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%
Critical illness	Symptoms of severe disease but intubated with respiratory failure, septic shock, and/or multiorgan dysfunction

Data has also shown that people from racial and ethnic minority groups face a higher risk of serious illness or death from COVID-19. These groups often have more than one medical condition and develop chronic medical conditions at a younger age [16].

Viruses change overtime because of mutations which sometimes can lead to variants. Although most variants do not heavily impact the properties of the virus, some may demonstrate an increase in transmissibility, clinical disease presentation, or an increase in virulence. Some variants may spread more easily resulting in a higher number of cases which can result in decreased effectiveness of public health and social measures or available vaccines, therapeutics, diagnostics. As of February 26th, 2022, there has been five COVID-19 variants of concern (VOC): Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Omicron (B.1.1.529), as described above, which have emerged around the world with clear evidence indicating a significant impact on transmissibility or rate of infection [5]. The new variants spread the same way as the original COVID-19, although, some of the new variants like Omicron are much more transmissible than the original and Delta. Even though it is much easier for Omicron to spread, data suggest it is generally less severe. However, the surge in cases can lead to a significant increase in the number of hospitalizations and death. The delta Variant has shown to be more contagious than earlier variants and may result in more severe cases [5].

Recommended inpatient laboratory evaluation for COVID-19

In Table 2 there are a few laboratory predictors that can help physicians determine the severity of a COVID positive patients' disease as well as help determine a poor outcome.

This can help doctors to begin efficient aggressive treatment without delay by adequately predicting severe/critical cases which will improve survival rates and reduce both illness and fatality in the COVID-19 pandemic. It is important to note that getting cut-off references values of significance for prediction COVID-19 case progression is not yet fully confirmed. However certain values brought up in a 2021 had been predicted and at what limit they would represent a severe case vs. a poorer prognosis (Table 3). Of these values a higher cut-off value of C-reactive protein (CRP), interleukin-6 (IL-6), LDH, neutrophil count, %PD-1 expression, D-dimer, creatinine, AST and cortisol are linked to severe and critical cases while low lymphocyte count, and low albumin level are also visible [5]. Other values that will appear elevated are CPK, ferritin, troponin, PT, serum amyloid A protein (SAA), liver function enzymes appearing 5x higher than normal and finally a ratio of absolute neutrophil count to absolute lymphocyte count > 3.5. All these lab results point towards a more severe course of infection.

Laboratory predictors in COVID-19 are shown in Table 3.

Table 2. Recommended Inpatient Laboratory Evaluation for COVID-19 [8, 17].

Diagnosis	• rRT-PCR (gold standard) • Antigen • Serology (antibody)	
Biochemistry	CBC (recommended daily check until it's stable)	• Leukocytes • Lymphocytes • Neutrophils • Platelets • Haemoglobin
	Coagulation factors (recommended daily check if it's elevated or patient in ICU)	• D-dimer • PT • aPTT
	Inflammatory factors	• CRP • ESR • Procalcitonin
	Liver functions	• ALT • AST • Bilirubin
	Kidney functions	• CK • Creatinine
	Lung injury	• LDH
	Cardiac injury	• Troponin
Radiology	• Chest CT	

Table 3. Laboratory predictors in COVID-19 positive patients for how severe/critical the condition will be, as well as for poor prognostic factors [18-21].

Laboratory indicators of COVID-19 progression into severe/critical condition	Mean upper limits for sever/poor prognostic factors	Normal lab values in healthy individuals
CRP	≥58.2 mg/L ± 47	0.0-8.0 mg/L
Neutrophil count	≥ 6.1 × 10^9/L ± 5.8	3000-5800 x 10^6 /L
T-lymphocyte count	≤ 0.8 × 10^9/L ± 0.46	0.64-1.18 × 10^9/L [22]
D-Dimer	≥12.9 μg/mL ± 52.7	< 0.5 μg/mL
%PD-1 Expression on T-cell	≥47± 24	none
IL-6	≥29.6 pg/mL ± 138	0-43.5 pg/ml [23]
Cortisol	≥794 nmol/L ± 264	170-635 nmol/L
AST	≥42.4 IU/L ± 19.5	0-35 units/L
Albumin	≤30.4 g/L ± 6.1	35-55 g/L
Creatinine	≥77.1 μmol/L ± 31.2	61.9-115 μmol/L
Lactate dehydrogenase (LDH)	382 U/L ± 221	45-90 U/L
Neutrophil-lymphocyte ratio (NLR)	> 3.5	0.78 - 3.53 [24]
Serum amyloid A Protein (SAA)	elevated	2.26 ± 1.66 mg/L [25]
Ferritin	elevated	15-200 ng/mL (15-200 μg/L)
Troponin	elevated	Troponin I — 0-0.5 ng/mL (0-0.5 μg/L) Troponin T — 0-0.10 ng/mL (0-0.10 μg/L)
PT	prolonged	11-13 s

Treatment and vaccines

Early diagnosis of COVID-19 is a cornerstone in optimizing the treatment regimen in patients with suspected COVID-19 disease. The date of onset of the first symptoms is the most important information when making a decision on treatment. The illness severity of COVID-19 disease can range from mild to critical.

Mild to moderate disease is defined as mild symptoms up to mild pneumonia, severe disease is defined as dyspnoea, hypoxia, or more than 50% lung involvement on imaging, and critical disease is defined as respiratory failure, shock or multiorgan dysfunction syndrome [26]. See Table 4 for details.

Table 4. Disease severity, risk of disease progression, setting and treatment of COVID-19.

Disease severity, risk of disease progression, setting	**Treatment**	**Comment**
Asymptomatic, not at high risk of disease progression, not hospitalized	**Not recommended** [27]	
Mild to moderate disease, not at high risk of disease progression, not hospitalized	**Not recommended** [27]	
Mild to severe disease, high risk of disease progression, not hospitalized	**Nirmatrelvir** 300 mg with **ritonavir** 100 mg (**Paxlovid**) orally twice daily x 5 days OR **Sotrovimab:** 500 mg single IV infusion OR **Remdesivir:** 200 mg IV day 1, then 100 mg IV day 2-3 OR **Molnupiravir:** 800 mg p.o. twice daily for 5 days [28]	eGFR > 60 mL/min. Administer therapy as early as possible in the course of disease: Paxlovid: 5 days Sotrovimab: 10 days Remdesivir: 7 days Molnupiravir: 5 days

Mild disease (no LRTD), high risk of disease progression, hospitalized	**Remdesivir:** Adult (weight > 40 kg): 200 mg IV on day 1, then 100 mg IV daily. Infuse each dose over 30-120 min. Paediatric (weight 3.5- 40 kg): 5 mg/kg IV on day 1, then 2,5 mg/kg IV daily. Duration: 5 days, if no clinical improvement at 5 days, extend to 10 days OR [29] **Monoclonal antibody**: if admitted for reason other than COVID-19 **Prophylactic anticoagulation** [30]	Monoclonal antibody should be administered as soon as possible, 7-9 days of symptoms.
Moderate disease (evidence of LRTD), patient at high risk of disease progression, hospitalized	**Remdesivir:** Adult (weight > 40 kg): 200 mg IV on day 1, then 100 mg IV daily. Infuse each dose over 30-120 min. Paediatric (weight 3.5- 40 kg): 5 mg/kg IV on day 1, then 2,5 mg/kg IV daily. Duration: 5 days, if no clinical improvement at 5 days, extend to 10 days OR [29] **Prophylactic anticoagulation** [30]	

Severe disease (requires supplemental O_2), hospitalized	**Remdesivir:** Adult (weight > 40 kg): 200 mg IV on day 1, then 100 mg IV daily. Infuse each dose over 30-120 min. Paediatric (weight 3.5- 40 kg): 5 mg/kg IV on day 1, then 2,5 mg/kg IV daily. Duration: 5 days, if no clinical improvement at 5 days, extend to 10 days OR [29] **Dexamethasone**: 6 mg IV once daily x 10 days ONLY for patients on supplemental oxygen or mechanical ventilation [32] **Tocilizumab:** 8 mg/kg up to 800 mg, given as single IV infusion. Second dose 12-24 hours later if no improvement. [31] **Therapeutic anticoagulation** [30]	
Critical disease (requires mechanical ventilation or ECMO), hospitalized	**Remdesivir:** Adult (weight > 40 kg): 200 mg IV on day 1, then 100 mg IV daily. Infuse each dose over 30-120 min. Paediatric (weight 3.5- 40 kg): 5 mg/kg IV on day 1, then 2,5 mg/kg IV daily. Duration: 10 days OR [29] **Dexamethasone:** 6 mg IV once daily x 10 days ONLY for patients on supplemental oxygen or mechanical ventilation [32] **Tocilizumab:** 8 mg/kg up to 800 mg, given as single IV infusion. Second dose 12-24 hours later if no improvement. [31] **Prophylactic anticoagulation** [30]	

Legend: LRTD - lower respiratory tract disease

Dynamics of COVID-19 pandemic

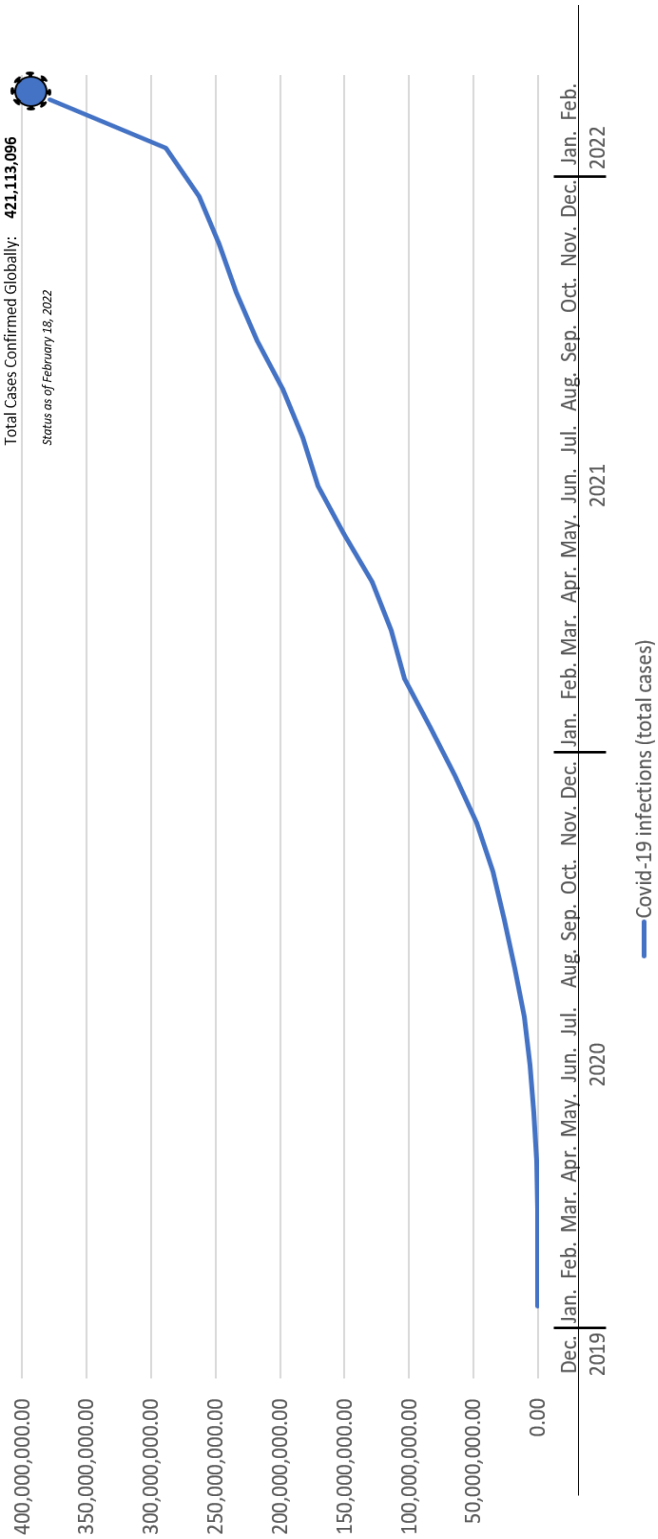

Figure 1. COVID-19 infections – total number of cases globally until February 18, 2022.

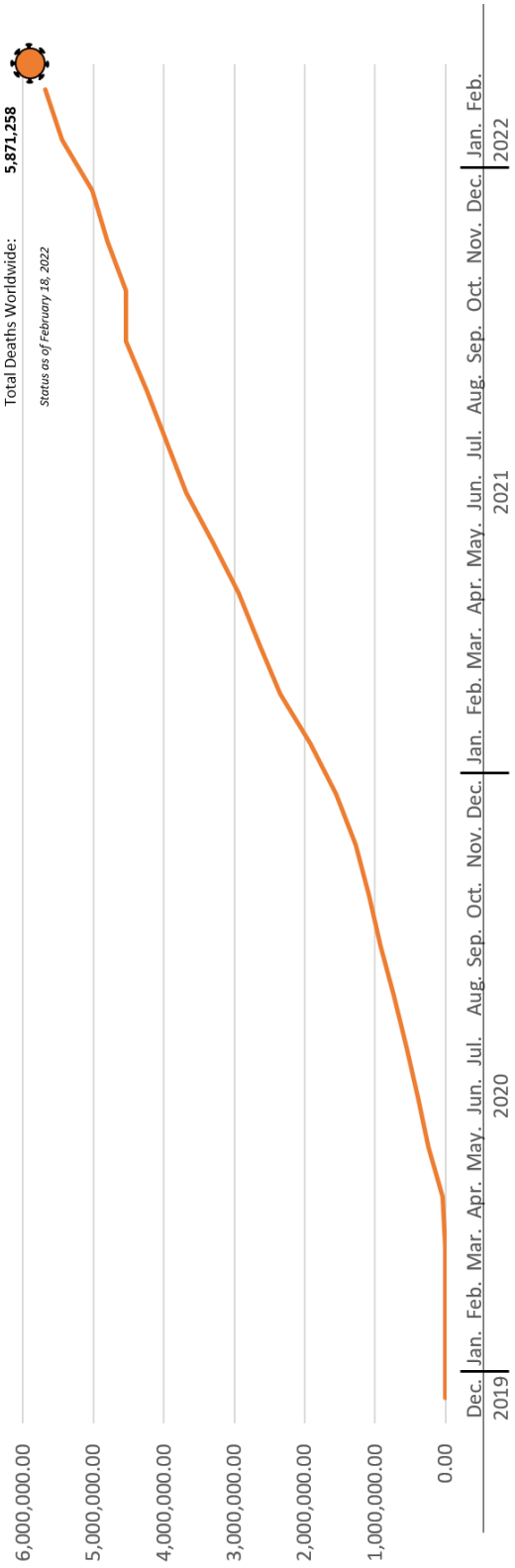

Figure 2. COVID-19 deaths – total global number until February 18, 2022.

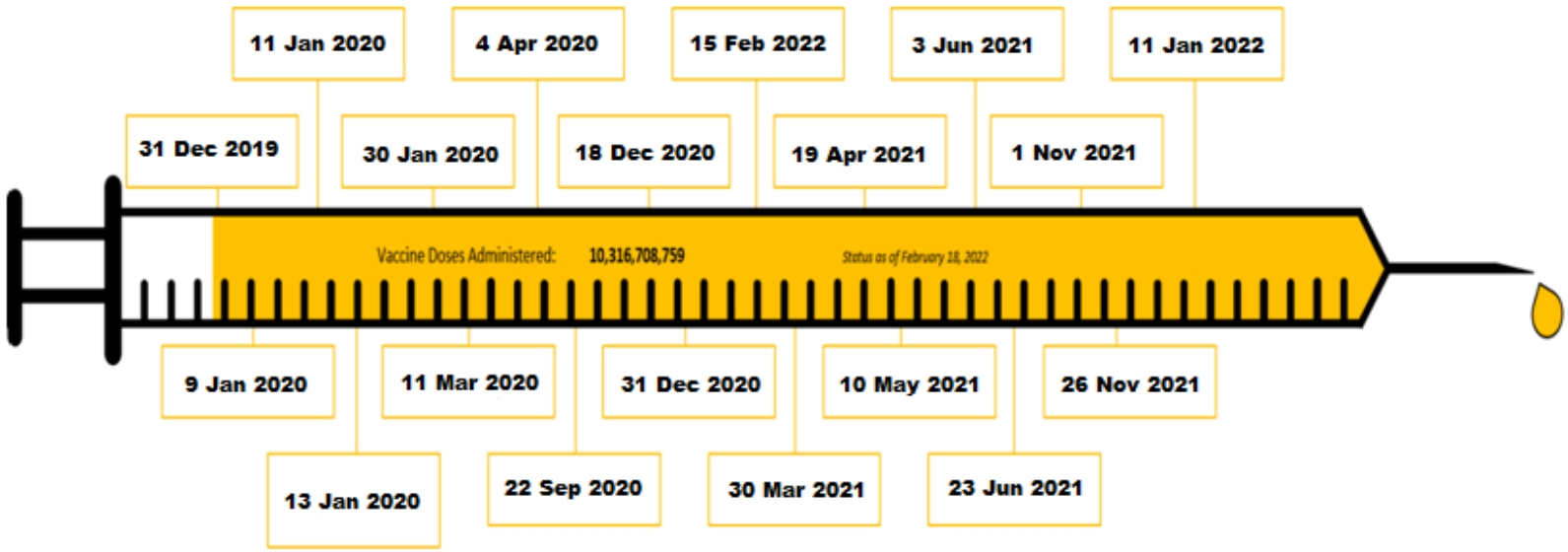

Figure 3. COVID-19 timeline until February 18, 2022. Legend: **31 December 2019** - Wuhan Municipal Health Commission, China, reported a cluster of cases of pneumonia in Wuhan, China; **9 January 2020** - WHO reported the Chinese authorities have concluded the outbreak in Wuhan is caused by a novel coronavirus, COVID-19; **11 January 2020** - Chinese media reports the first death resulting from the new coronavirus strain; **13 January 2020** - Thailand reports first documented imported case of COVID-19 from Wuhan, the first recorded case outside the People's Republic of China; **30 January 2020** - The Director General of the WHO declared the new coronavirus outbreak a public health emergency of international concern; **11 March 2020** - WHO makes the assessment that the novel coronavirus should be characterized as a pandemic; **4 April 2020** - WHO reports over one million cases of COVID-19 worldwide; **22 September 2020** - WHO issued the first rapid diagnostic test for detecting the SARS-COV-2 virus; **18 December 2020** - South Africa reports the detection of a new variant of SARS-COV-2 spreading rapidly around South Africa; **31 December 2020** - WHO issued its first emergency use validation for a COVID-19 vaccine; **15 February 2021** - WHO authorizes the AstraZeneca/Oxford University vaccine for emergency use; **30 March 2020** - WHO report states that animal-to-human transmission was most likely the origin of the virus; **19 April 2021** - Deaths due to coronavirus surpass 3 million globally; **10 May 2021** - WHO classifies the Delta variant discovered in South Africa as a global variant of concern; **3 June 2021** - One billion doses of COVID-19 vaccines administered globally; **23 June 2021** - Approximately 10% of the global population is vaccinated against COVID-19; **1 November 2021** - Johns Hopkins University reports that COVID-19 has killed more than five million people globally in less than two years; **26 November 2021** - WHO classifies the Omicron variant of SARS-COV-2 a concern; **11 January 2022** - WHO states that over half of the population in Europe would become infected with Omicron in the following 6-8 weeks.

COVID-19 dynamics by country

USA

As seen in Table 5, in the United States of America, the first COVID-19 case was reported on January 21, 2020 [32]. The date of the first recorded death was on February 29, 2020 [33a-b]. By February 10, 2022, there have been a reported total of 77 million cases and about 910 000 deaths due to COVID-19 [34]. As of September 27, 2022, there have been a reported total of 96.16 million cases and a reported total of 1.06 million deaths due to COVID-19 [85]. The date of the first administered dose of a COVID-19 vaccine to a member of the public was on December 14, 2020 [35]. By February 10, 2022, there have been 545,000,000 vaccine doses administered [36]. 80.6% of the population aged 5 and older has received at least one dose of the COVID-19 vaccine [34]. As of September 20, 2022, 616.17 million vaccine doses have been administered [86]. All data mentioned are current as of September 27, 2022.

Poland

As seen in Table 5, the first reported COVID-19 case in Poland was on March 4, 2020 [37]. The first reported death due to COVID-19 occurred on March 12, 2020 [38]. By February 11, 2022, in Poland there have been a total of 5,348,182 reported COVID-19 cases and a total of 107,757 reported deaths due to COVID-19 since March 4, 2020 [39]. As of September 27, 2022, there have been a reported total of 6.28 million cases and a reported total of 117,481 deaths due to COVID-19 [87]. The first administered dose of a COVID-19 vaccine was given to the general public on December 27, 2020. By February 11, 2022, a total of 52,531,873 doses of COVID-19 vaccines have been administered in Poland, with approximately 57.9% of the population considered to be fully vaccinated in Poland [40, 41]. As of September 26, 2022, 56.64 million vaccine doses have been administered [88]. All data mentioned are current as of September 27, 2022.

United Kingdom

As seen in Table 5, in the United Kingdom (UK), the first COVID-19 case was reported on January 31, 2020 [42]. The date of the first recorded death was March 4, 2020 [43]. By February 8, 2022, there have been a reported total of about 18 million COVID-19 cases and 159 000 deaths due to COVID-19 [44]. As of September 27, 2022, there have been a reported total of 23.62 million cases and a reported total of 206,532 deaths due to COVID-19 [89]. The date of the first administered dose of a COVID-19 vaccine to a member of the public was on January 11 2021 [45]. By February 8, 2022, there have been around 116,000,000 vaccines administered [45]. In the last seven days of February 7, 2022, the current rate of infection in the UK was 2009 cases per 100 000 population [44]. As of February 2022, the Faroe Islands have the highest seven day rate of infections in Europe with 8,606 [44]. As of September 4, 2022, 151.25 million vaccine doses have been administered [90]. All data mentioned are current as of September 27, 2022.

South Africa

As seen in Table 5, the first COVID-19 case in South Africa was reported on March 5, 2021

[46]. The date of the first recorded death was March 27, 2020 [47]. By February 10 2022, there have been a reported total of 3,6 million cases and about 97 000 deaths due to COVID-19 [48]. As of September 27, 2022, there have been a reported total of 4.02 million cases and a reported total of 102,149 deaths due to COVID-19 [91]. The date of the first administered dose of a COVID-19 vaccine was on February 17, 2021 when it was administered to healthcare workers [49]. By February 10, 2022, there have been about 19.87 million vaccines administered [50]. Additionally, 3.5 million individuals with COVID-19 have recovered [48]. As of September 27, 2022, 37.62 million vaccine doses have been administered [92]. All data mentioned are current as of September 27, 2022.

Japan

As seen in Table 5, in Japan, the first COVID-19 case was reported on January 16, 2020 [51]. The date of the first recorded death was February 13, 2020 [52]. By February 10, 2022, there have been a reported total of about 3,6 million cases and about 20,000 deaths due to COVID-19 [53]. As of September 27, 2022, there have been a reported total of 21.15 million cases and a reported total of 44,580 deaths due to COVID-19 [93]. The date of the first administered dose of a COVID- 19 vaccine was on February 21, 2021, administered to healthcare workers [54]. By February 10, 2022, there have been 101,48 million vaccines administered [54]. By February 10, 2022, there have been about 872,000 active COVID-19 cases and 2,7 million of recovered cases [55]. As of September 27, 2022, 323.39 million vaccine doses have been administered [94]. All data mentioned are current as of September 27, 2022.

Brazil

As seen in Table 5, in Brazil the first COVID-19 case was reported on February 25, 2020 from an individual who had recently returned from Italy [56]. The date of the recorded death was March 17, 2020 in Sao Paulo, Brazil [57]. By February 10, 2022, there have been a reported total of 27 million cases and 636 000 deaths due to COVID-19 [58]. As of September 27, 2022, there have been a reported total of 34.64 million cases and a reported total of 685,835 deaths due to COVID-19 [95]. The date of the first administered dose of a COVID-19 vaccine to a member of the public was on December 27, 2020 [59]. By February 10, 2022, there have been 353,813,623 vaccines administered [60]. As of September 27, 2022, 472.85 million vaccine doses have been administered [96]. All data mentioned are current as of September 27, 2022.

Germany

As seen in Table 5, the first reported COVID-19 case in Germany was on January 27, 2020 [61]. The first reported death due to COVID-19 occurred on March 9, 2020 [62]. By February 11, 2022, in Germany there have been around 12,070,000 reported COVID-19 cases and a total of 119,685 reported deaths due to COVID-19 since January 27, 2020 [63]. As of September 27, 2022, there have been a reported total of 33.14 million cases and a reported total of 149,714 deaths due to COVID-19 [97]. The first administered dose of

a COVID-19 vaccine was given to the general public on December 27, 2020 [63]. By February 11, 2022, a total of 166,690,548 doses of COVID-19 vaccines have been administered in Germany, with approximately 74% of the population considered to be fully vaccinated in Germany [41, 63]. As of September 26, 2022, 185.42 million vaccine doses have been administered [98]. All data mentioned are current as of September 27, 2022.

China

As seen in Table 5, in China the first COVID-19 cases were reported in December 2019. In December of 2019 clusters of cases of a pneumonia caused by a novel coronavirus were being reported out of Wuhan, China. [64] The date of the first reported death due to COVID-19 was on January 11, 2020, in Wuhan. The 61-year-old male patient had been admitted to the hospital before his death. [65] As of February 10, 2022, there have been a reported total of 97,607 cases and 4,636 deaths due to COVID-19. As of September 27, 2022, there have been a reported total of 988,427 cases and 5,226 deaths due to COVID-19. [66] The date of the first administered dose of a COVID-19 vaccine to a member of the public occurred around December 2020. Currently, as of February 10, 2022 [99], there have been 2.1 billion vaccines administered as of August 26, 2021 [100]. All reported data is current as of September 27, 2022; however, there is a possibility that the numbers have been underreported. [64, 65, 66].

Table 5 shows COVID-19 statistics for selected countries.

Table 5. Selected COVID-19 country statistics. All data are current as of September 27, 2022.

Country	Population	Date of 1st reported case	Date of 1st reported death	Cumulative deaths	Cumulative cases	Total vaccine doses admin (#)	1st vaccination date
Brazil	215 million	February 25, 2020	March 17, 2020	685,835	34.64 million	472.85 million	January 17, 2021
China	1.402 billion	December 2019	January 11, 2020	5,226	988,427	2.1 billion	December 2020
Germany	84.21 million	January 27, 2020	March 9, 2020	149,714	33.14 million	185.42 million	December 27, 2020
Japan	125.86 million	January 16, 2020	February 13, 2020	44,580	21,15 million	323.39 million	February 17, 2021

Poland	37.78 million	March 4, 2020	March 12, 2020	117,481	6,28 million	56.64 million	December 27, 2020
South Africa	60.544 million	March 5, 2020	March 27, 2020	102,149	4.02 million	37.62 million	February 17, 2021
United Kingdom	68.466 million	January 31, 2020	March 4, 2020	206,532	23.62 million	151.25 million	January 11, 2021
USA	334.14 million	January 21, 2020	February 29, 2020	1.06 million	96.6 million	616.17 million	December 14, 2020

Discussion

The graphs presented in the Dynamics section depict the total number of COVID-19 infections worldwide. Although it is not possible to determine how the first infections of SARS-COV-2 came about, the first visible case was seen on December 31st, 2019, in Wuhan, China when the Wuhan Municipal Health Commission reported numerous incidences of a 'viral pneumonia'. By the 21st of January, there was evidence of the possibility of human to human transmission of the virus. The United States of America also reported its first confirmed case of the novel coronavirus on this date. On the 24th of January, France informed the WHO of three cases of the novel coronavirus, all of whom had travelled from Wuhan. These were the first confirmed cases in the European region. By the end of January, Thailand, Japan, South Korea, Taiwan, Hong Kong, Macau, Singapore, Vietnam, France, Nepal, Australia, Canada, Malaysia, Cambodia, Germany, Sri Lanka, Finland, United Arab Emirates, India Italy, Philippines, Russia, Spain, Sweden and the United Kingdom had all confirmed the first incidence of COVID-19. The World Health Organization declared the outbreak a Public Health Emergency of International Concern on the 30 January 2020. On the 11th of February, the WHO announced that the disease caused by the novel coronavirus would be named COVID-19. On the 7th of March, 2020, the global confirmed COVID-19 cases surpassed 100,000 and the WHO issued a statement calling for action to stop, contain, control, delay and reduce the impact of the virus at every opportunity. On the 11th of March, after being deeply concerned by the alarming levels of spread and severity, and by the alarming levels of inaction, WHO made the assessment that COVID-19 could be characterized as a pandemic. On the 13th of March, Europe became the epicentre of the pandemic with more reported cases and deaths than the rest of the world combined, apart from the People's Republic of China. By the 4th of April, 2020, there were over 1 million cases of COVID-19 that had been confirmed worldwide, a more than tenfold increase in less than a month. On the graph (Figure 1), one may observe a

consistent increase in the number of cases until December 2021. On the 22nd of September, 2020, the WHO issued the first rapid diagnostic test for detecting the SARS-CoV-2 virus. On the 18th of December 2020, South Africa announced the detection of a new variant of COVID-19 rapidly spreading. With the introduction of vaccinations, the WHO issued its first emergency use validation for a COVID-19 vaccine on the 31st of December 2020. On the 5th January 2021, Pfizer/BioNTech vaccine was the first to receive an emergency use validation from WHO for efficacy against COVID-19. On the 15th of February 2021, the AstraZeneca and Oxford COVID-19 vaccine was permitted for emergency use.

The 19th of April 2021 marked the day where the death rate due to coronavirus surpassed 3 million globally. On the 10th of May the WHO classified the Delta variant as a global variant of concern. On the 3rd of June 2021 the world reached 1 billion vaccine doses. In the months of January and February 2022, we observed a much larger number of global infections reaching up to 3.8 million per day in late January [67, 68].

The graphs presented in the Dynamics section (Figure 1) show an increase of global cases starting from March 2020, where it is visible a steady exponential growth from April 2020 to November 2020 reaching 50M. Starting November the amount of cases increased linearly until January 2022 after which there was a large spike from 300M to 400M of total confirmed cases. When looking at the mortality rates (Figure 2), a similar pattern can be observed but at a smaller scale. Beginning in April of 2020 there is a linear growth of the number of deaths reaching close to 6M by February 2022. Interestingly there is a plateau from September to October 2021 at around 4.5M where the amount of deaths seems to stay stagnant, after which the linear growth continues.

According to Statista, the country with the highest number of cases is the United States of America as of February 2022, with almost 77,179,255 cases. This is approximately 23% of the total population in the USA. Of these cases, the number of deaths due to COVID-19 is around 1.2% of total cases. The second-largest number of cases worldwide may be seen in India and the third place belongs to Brazil, with case numbers rounding to 43M and 30M respectively. With the number of deaths, USA continues to stand on top with around 900,000 due to COVID-19. Brazil is right after USA, with 650,000 and finally India with 500,000 deaths. From the few countries presented in this article, the country with the largest amount of cases in comparison with the population size was in the United Kingdom with around 27% of the population getting infected with COVID-19 from January 2020 to February 2022. The countries with the highest percentage of COVID-19 positive patients dying of COVID-19 were South Africa with 3% and Poland and Brazil both with 2% (Table 6).

Table 6. Selected countries showing the percentage of infected persons vs. the percentage of deaths from COVID-19 [69, 70].

Country	Percent of the total population who have contracted COVID-19 (total COVID-19 cases / total country's population)	Percentage of deaths from COVID-19 (total deaths by COVID-19 / total COVID-19 cases)
USA	23%	1.2%
Poland	14%	2%
UK	27%	0.9%
South Africa	6%	3%
Japan	3%	0.5%
Brazil	13%	2%
Germany	14%	1%
Italy	20%	1.3%

Conclusions

Updated global numbers of cases vs. deaths for COVID-19 around the time of publication of this article (12 September 2022) show 613,972,905 cases and 6,516,982 deaths [69, 70].

Since the primary outbreak of SARS-CoV-2 in November 2019, there has been an ongoing race to find the appropriate treatment and how to reduce the spread of the virus most effectively. Viruses are under constant replication inside a living organism, and through mutations, the coronavirus has evolved from a primary virus to a family of many variants of different severity.

To this date, the main ways to develop protection against the virus is immunization through either vaccination or by being infected by the virus [71]. Although many viruses cause

a post-infected immunization it has shown that individuals can be re-infected up to many times by the coronavirus. Due to this, the Centers for disease Control and Prevention (CDC) have recommended vaccination for individuals previously infected [71].

The arrival of SARS-CoV-2 in 2019 caused an immediate need for vaccines. Due to the sudden demand, the Food and Drug Administration (U.S. FDA) approved vaccines faster and with less scientific support than previously required. Due to this fact, vaccines previously approved are not necessarily used at present [72]. As of today, there are three FDA approved COVID-19 vaccines in the United States, namely: Pfizer-BioNTech, Moderna and Janssen/Johnson & Johnson [73]. Novavax and Oxford-AstraZeneca are highly distributed COVID-19 vaccines in various countries, but are currently not FDA approved in the US [74].

How the COVID-19 vaccines work against the virus and novel variants

All COVID-19 vaccines that have passed phase 3 clinical trials and been approved for use generally showed a high level of safety and efficacy against the original virus strain [75]. The efficacy, side effects and adequacy over time varied, but they were assumed as safe and beneficial to decrease transmission, serious infection and death.

Phase 3 clinical study is a strictly controlled and randomized trial used to evaluate the COVID-19 vaccines. In this primary clinical study, the safety and efficacy of the vaccine are being assessed and crucial data are presented before distribution. Regarding prevention of symptomatic disease, both Pfizer-BioNTech and Moderna showed an efficacy of around 95% in their Phase 3 clinical study, which constitutes the highest percentage among the vaccines. Janssen/Johnson & Johnson had an efficacy of 66%, while the two non-FDA approved vaccines Oxford-AstraZeneca and Novavax showed an efficacy of 76% and 90% respectively [76]. The efficacy presented is after receiving two vaccine doses and is assessed against symptomatic COVID-19 infection.

Multiple clinical trials have been conducted for the vaccines and are described in a comprehensive online article on UpToDate. There, the calculated efficacy is being tested and effectiveness of the vaccines evaluated supported by the numbers, but it also shows decreased effects over time [77].

New variants

A highly discussed topic lately, is if the effectiveness of the vaccines previously presented also includes novel variants of the SARS-CoV-2 virus. Mutations of the primary virus have resulted in new variants and concern of immune escape has developed. Some of the new variants are described as more contagious and more fatal [78].

As described, none of the COVID-19 vaccines assure 100% effectiveness against the virus and data show that breakthrough infections are more common with novel variants, such as with Omicron and the Delta virus. Data also indicate that vaccinated individuals have a reduced risk of developing serious disease if both infected and re-infected. As a safety

measure, vaccine booster doses have been introduced and show an increased vaccine effectiveness over a short period of time and decreased transmission risk [77].

As stated by UpToDate, data suggest that the vaccine effectiveness is reduced for symptomatic disease for both Omicron and the Delta variant in comparison to the original strain, but on the other hand the benefit of vaccination is clearly stated with an effectiveness against hospital-related infections of 94% for the Delta variant and 90% for Omicron regarding the mRNA-vaccines [77]. Furthermore, there is clear evidence that the vaccines decrease the risk of serious disease regarding the novel variants as well, but the evidence of avoiding symptomatic disease is of various degrees.

As the COVID-19 pandemic will eventually come to pass, we should already be aiming our focus on the next pandemic. If the past is any predictor of the future, another respiratory virus of zoonotic origin is highly probable [79]. Each year, the WHO commissions an expert committee to update a shortlist of pathogens used to highlight the danger and prioritize research which lacks effective treatment [80]. SARS-CoV-2 was added to the list in the latest version for obvious reasons, as a lot of effort has gone into research on this virus. A part of the list which should receive more attention is what is listed as the last part of the list, which states: Disease X. This is the part at the end of the list representing a pathogen currently unknown to produce human disease as potentially the cause of the next pandemic [80]. Regardless of multiple recent efforts to predict and manage emerging infectious disease, we failed to foresee the pathogens causative of the pandemics in 2009 and 2020 [81]. So, if we have learned anything from the last decade is that we should be quicker to identify and implement strategies not only when, but even before these diseases arise.

We know what implementations are required to limit the impact of a pandemic. WHO assembled a list of steps needed to control a pandemic based on lessons learned after the SARS-pandemic. Early reporting of cases, global scientific sharing and cooperation, limiting travel and stockpiling of PPE equipment are only some, but they are all still applicable today [82].

However, in the forefront of the discussion in the scientific community now is the prevention of spillover, which is the process where a pathogen crosses the animal-human host barrier. Essentially, preventing spillover is to stop pandemics before they become pandemics. Although we have some organizations researching this in place, such as the Global Virome Project [83], many claim the time for establishing a sustained, multisectoral global viral surveillance network is now [84]. A One Health approach, integrating formulation, funding, implementation, and governance of policies involving human, animal and wildlife populations are thought to be the ideal way to tackle the problem of spillover [81]. There have been suggestions to further specify this approach by focusing it on hotspots where spillover is more likely to occur [81]. In any way, attempting to get ahead of the next possible pandemic is key in our efforts to lessen health and socioeconomic impact on the world.

Preparedness key points

1. **More pandemics will appear.** Be prepared. COVID-19 will not be the last new disease to take advantage of modern global conditions. Continued vigilance is vital. Preparation includes enhancing the integration and effectiveness of the public health, healthcare, and emergency management systems through education, supplying adequate provisions, and drills as well as developing incentives (e.g., tax credits, identified cost savings) that increase the number of nongovernmental entities engaged in actions that enhance their communities' health security.
2. **Report cases early.** Global health security requires promptly identifying and reporting cases of any disease with the potential for international spread. Concealing these cases or denying that they exist carries the potential for enormous human suffering and death, loss of international credibility, negative domestic and regional economic impact, and a very real risk the outbreak will spiral out of control.
3. **Alert the world.** As soon as an emerging and transmissible infection is confirmed, international bodies, such as WHO, must issue a global alert through all available communication modalities.
4. **Promote international scientific collaboration.** The world's scientists, clinicians, and public health experts must act collaboratively to investigate, control, and, if possible, eliminate the disease.
5. **Provide leadership and consistency.** Coordinating messages and policy among federal, state, and local health officials and affected institutions is critical to avoiding contradictions and confusion that can undermine public trust and impede containment measures. To build public trust and cooperation, provide continuous, accurate, and science-based information on what is known and not known about the disease. Information should be technically correct and sufficiently complete to support policies and actions without being patronizing. Minimize duplication of, and ensure coordination between federal, state, local, and tribal authorities.
6. **Avoid speculation.** During an outbreak, limit officially disseminated information to specific data and results; messages should omit speculation, over-interpretation of data, overly confident assessments of investigations and control measures, and comments related to other jurisdictions. Rumours, misinformation, misperceptions, and stigmatization of affected groups must be addressed promptly and definitively.
7. **Provide safety guidelines.** It is essential to provide guidance to the public on actions to take to protect themselves and their family members and colleagues. Assess healthcare system cyber security and develop alternative plans for any cyber incidents.
8. **Institute travel limitations and screening.** Implement appropriate travel restrictions and airport screening to contain the international spread of an emerging infection. Airport screening may include passive passenger screening using questionnaires or sophisticated infrared equipment to screen all passengers for fever and indications of possible exposure, as well as health worker-conducted interviews.
9. **Implement early and consistently support containment, testing, and aggressive contact tracing.** In the absence of a curative drug or preventive vaccine,

well-known public health interventions can effectively contain an outbreak. The methods include active surveillance of suspected contacts, self-surveillance by contacts who voluntarily isolated themselves, and widespread testing, social distancing, and quarantine.

10. **Stockpile necessary medications and equipment.** Enhance the national capability to produce and effectively use both medical countermeasures and non-pharmaceutical interventions, including those needed for both the acute and the chronic conditions.
11. **Bolster national healthcare infrastructures.** A high priority is improving existing healthcare systems' weaknesses that permit emerging infections to amplify and spread and that can compromise patient care. This includes having adequate materials and capacity for expected surges of infected patients, including hospitals and other healthcare facilities.
12. **Protect healthcare workers.** The people at greatest risk for contracting the disease are health workers, including first responders. This requires working with professional societies to improve strategies (including PPE use) to protect healthcare workers. Special vigilance must be paid to women, who staff the lower ranks of health personnel in many countries.
13. **Do just-in-time professional education.** Educate healthcare workers and public health staff on appropriate strategies to recognize the disease and to implement control measures.
14. **Prepare the public.** Recognize that preparation for and control of pandemics are extremely disruptive and consume enormous resources at levels that might not be sustainable over time.

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Authors' affiliations:
[1] Jagiellonian University Medical College, School of Medicine in English, Cracow, Poland

Corresponding author:
Silja Lea
św. Sebastiana 22/4
31-049 Kraków
Poland
E-mail: siljalea98@gmail.com
Phone: (+47) 41356157

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