Sonderausgabe III
SARS-CoV-2/
COVID-19
April 2020

GyNews

Offizieller Newsletter der Universitätsklinik für Gynäkologie und Geburtshilfe Innsbruck

Liebe Kolleginnen und Kollegen,

testen, testen, testen!
Gebetsmühlenartig wird das Mantra der Regierung wiederholt. Manche Krankenhäuser haben daraufhin vorauseilend auch eine Testung aller aufzunehmenden PatientInnen begonnen. In Innsbruck ist das (noch) nicht der Fall. Mehrfach habe ich den Vorwurf gehört, wir würden dadurch PatientInnen aber vor allem MitarbeiterInnen gefährden. Als Frauenärztinnen und Frauenärzte kennen wir uns bei Screeningtests schon ein wenig aus und können sie auch gut beurteilen. Während wir beim PAP-Test Sensitivität und Spezifität kennen, sind diese Kenngrößen für den COVID-Test noch weitgehend unbekannt. Es wird derzeit eine Spezifität um die 95% und eine ähnliche Sensitivität von 94% angenommen. Wir glauben aufgrund der Studie des SORA-Instituts weiters, dass die Prävalenz von COVID-positiven Personen außerhalb der Hotspots wie Ischgl sehr gering ist (am 10. April 0,33% in Österreich). Wahrscheinlich ist diese Prävalenz zwischenzeitlich weiter gesunken. Das bedeutet, dass man mindestens 300 asymptomatische Personen testen muss, um ein positives Ergebnis zu erhalten. Bei einer Sensitivität von 94% werden infizierte PatientInnen natürlich übersehen und falls der Test im diagnostischen Fenster durchgeführt wurde, können wir uns nicht sicher sein, dass die negativ getestete Person am nächsten Tag nicht infektiös geworden ist. Umgekehrt bestimmen wir mit dem Test nicht infektiöse Viren, sondern nur die Virus-RNA. Wir können also gar nicht mit Sicherheit annehmen, dass die nachgewiesene RNA Teil von aktiven Viren ist und die Person somit auch infektiös ist.

Selbstverständlich ist die Situation bei symptomatischen Personen und deren Kontaktpersonen anders. Da muss bei positivem Test nahezu ausnahmslos eine Infektiosität angenommen werden. Das Testen dieser Personen macht also zweifellos großen Sinn und ist eine wichtige Grundlage für die Eindämmung der Infektionsausbreitung. Aber das lückenlose Screening von asymptomatischen PatientInnen bei der stationären Aufnahme wiegt uns in einer falschen Sicherheit und erinnert mich sehr an die Situation als AIDS aufkam. Als die HIV-Infektion bekannt wurde, traten ähnliche Panikreaktionen auf, und wir mussten alle stationären Patientinnen testen: keine Operation ohne negativem HIV-Test. Inzwischen macht das wohl niemand mehr, obwohl es HIV weiterhin gibt. So wird es auch mit COVID sein.

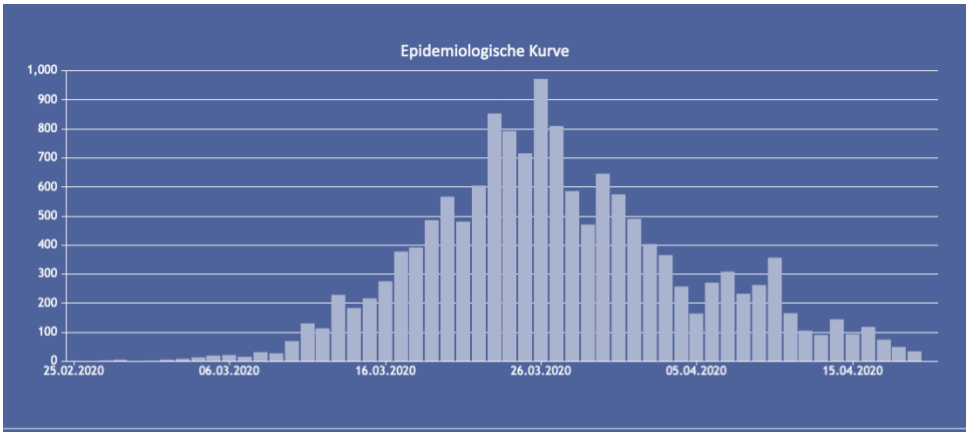
Die Erkrankung wird wohl in der nächsten Zeit nicht verschwinden und wir sollten unsere Energie viel mehr für Strategien zum bestmöglichen Umgang mit der Situation und nicht für das flächendeckende Testen verwenden. Wir werden unsere Patientinnen wohl auf lange Zeit (vielleicht für immer) nicht mehr mit Handschlag begrüßen und größeren Abstand halten. Unsere Wartezimmer in den Ordinationen werden sich wandeln und nur mehr einzelne Patientinnen auf die Untersuchung warten können. Das Abfragen von COVID-Symptomen wird Teil unserer Anamnese werden. Viele liebgewonnene Rituale wie etwa Chefvisiten oder Morgenbesprechungen mit dem ganzen Team wird es nicht mehr geben – aufgrund der ohnehin fraglichen Effizienz werden es wahrscheinlich maximal die Chefs vermissen. Viele Fortbildungsveranstaltungen werden in andere Formate umgewandelt werden. Ich durfte kürzlich für die ESGO ein Live-Webinar zum Endometriumkarzinom abhalten. 400 internationale TeilnehmerInnen konnten folgen und auch Fragen stellen. Die ganze Veranstaltung wird noch auf der E-Learning Plattform zum Download zur Verfügung stehen. Alles vom heimischen Laptop aus ohne lange Anreise. Nächste Woche nehme ich am amerikanischen Krebsforschungskongress AACR teil. Erstmals ohne Transatlantikflug, stundenlangem Warten an der Immigration, Jetlag und amerikanischem Essen. Ich werde dem virtuellen Meeting ganz einfach vom Schreibtisch aus folgen können.

Ich bin überzeugt, dass einige dieser Formate bleiben werden und unsere Gewohnheiten nachhaltig ändern werden. Die COVID-Pandemie bietet auch neue Chancen.

Univ. Prof. Dr. Christian Marth

Überblick: Das Neueste in Kürze

- Die Zahlen in Österreich folgen bisher einem erfreulichen Trend: Unter den **14.713** bestätigten Fällen, finden sich bereits **10.501 Genesene.**
- **Weltweit** wurden bisher insgesamt **2.404.325** bestätigte Fälle bekannt gegeben, 624.725 Menschen haben sich wieder erholt.
  (Stand 20.04.2020,10:00)



Die epidemiologische Kurve zeigt den tatsächlichen Zuwachs an positiv getesteten Personen. Sie ist eine Möglichkeit die Ausbreitungsdynamik einer Epidemie im Zeitverlauf darzustellen. Die Zuordnung zu einem Datum erfolgt je nach Verfügbarkeit der Informationen in folgender Reihenfolge: Erkrankungsdatum > Diagnosedatum > Meldedatum. Die Daten stammen aus dem Epidemiologischen Meldesystem.

Bundesland	Bgld.	Ktn.	NÖ	OÖ	Sbg.	Stmk.	T	Vbg.	W	Österreich gesamt
Bestätigte Fälle (Stand 20.04.2020, 08:00 Uhr)	302	394	2.479	2.203	1.200	1.653	3.425	858	2.199	14.713
Todesfälle[1] (Stand 19.04.2020, 09:30 Uhr)	8	10	82	38	29	101	85	9	90	452
Genesen (Stand 19.04.2020, 09:30 Uhr)	198	302	1.560	1.847	929	809	2.526	715	1.615	10.501
Hospitalisierung*[2] (Stand 19.04.2020, 09:30 Uhr)	16	15	196	95	88	117	112	19	159	817
Intensivstation*[3] (Stand 19.04.2020, 09:30 Uhr)	5	9	40	29	16	18	49	7	31	204
Testungen[4] (Stand 19.04.2020, 09:30 Uhr)	2.357	7.268	19.112	29.696	14.386	19.749	42.019	7.400	37.256	179.243

[1] Jede verstorbene Person, die zuvor COVID-positiv getestet wurde, wird in der Statistik als „COVID-Tote/r" geführt, unabhängig davon, ob sie direkt an den Folgen der Viruserkrankung selbst oder „mit dem Virus" (an einer potentiell anderen Todesursache) verstorben ist.

* Die Daten zur Hospitalisierung und Intensiv-Versorgung werden regelmäßig von den Landessanitätsdirektionen erhoben und einmal täglich bereitgestellt.

[2] Die Zahl „hospitalisiert" ist die Gesamtzahl aller zum Meldezeitpunkt in Krankenhausbehandlung befindlicher COVID-Patientinnen und Patienten im jeweiligen Bundesland.

[3] Die Zahl „Intensivstation" ist die Gesamtzahl aller zum Meldezeitpunkt auf einer Intensivstation behandelten COVID-Patientinnen und Patienten im jeweiligen Bundesland.

[4] Die Zahl „Testung" ist die Gesamtzahl aller durchgeführten Covid-Testungen. Die Daten dafür werden großteils von den durchführenden Laboren gemeldet.

Lagebericht von der Frauenklinik Innsbruck

Die Stationen kehren langsam wieder zu Normalbetrieb zurück, Ärzte und Ärztinnen bringen ihre Expertise in Prävention und Erforschung ein.

Dank ausgefeilter Vorsichtsmaßnahmen und Sicherheitssystemen, die vor allem durch die Gyn-COVID Beauftragte des Landes Tirol Dr. Alexandra Ciresa-König erstellt wurden, ist die Situation bei uns außerordentlich ruhig und unter Kontrolle.

Zwei positiv getestete Mitarbeiterinnen aus dem Pflegebereich wurden bereits im Vorfeld erkannt und es kam zu keiner Ansteckung von Patientinnen oder anderer MitarbeiterInnen.

Durch genaue Anamnese konnte eine Infektion bei einer Mammakarzinompatientin präoperativ erkannt und positiv getestet werden.

Der zum COVID-Bereich umgestaltete Kreißsaalbereich und die Geburtshilfestation kann dank rückläufiger Erkrankungszahlen ab nächster Woche wieder verkleinert und damit allgemein genutzt werden.

Patientinnen, deren Operationen wegen der Pandemie verschoben wurden, werden wir verständigen und ihnen neue Termine anbieten.

Die Ambulanz kann nur langsam wieder hochgefahren werden. Auch diese Struktur steht Ihnen in den nächsten Wochen für Zuweisungen wieder in vollem Umfang zur Verfügung.

Früherkennungsmammographien sind an der Radiologie/am BGZ wieder möglich.

Wir sind sehr froh, dass es uns gelungen ist trotz der sehr schwierigen Situation weiterhin Patientinnen in Studien zu rekrutieren und damit auch Zugang zur Spitzenmedizin und innovativen Behandlungsformen zu gewährleisten.

Ein Protokoll von Dr. Samira Abdel Azim wurde von der Ethikkommission genehmigt und wir planen durch Untersuchungen an Plazenta und Fruchtwasser einen Beitrag zur Erforschung der vertikalen Transmission und geburtshilflichen Problematik der COVID-Infektion zu leisten.

Die wichtigste Vorsichtsmaßnahme bleibt in jedem Fall das Bewahren von Abstand sowie geeignete Handhygiene! Das gilt für Ambulanzen und Stationen in Krankenhäusern genauso wie für Wartezimmer in Praxen.

Informationen in verschiedenen Sprachen

Das gesammelte Informationsmaterial und alle Links finden Sie hier

Damit sie auch anderssprachigen Patientinnen und ihren Angehörigen ausreichend Informationen zum neuartigen SARS-Cov-2-Virus und den damit zusammenhängenden Vorsichtsmaßnahmen liefern können, hat das Bundesministerium für Soziales, Gesundheit und Pflege, Informationsblätter in verschiedenen Sprachen verfasst. Diese können Sie hier aufrufen:

Englisch:

Allgemein

Protective measures against the coronavirus

Protective measures against the coronavirus – respiratory hygiene

Protective measures against the coronavirus – eyes, nose, mouth

Protective measures against the coronavirus – social distancing

Protective measures against the coronavirus – hands

Protective measures against the coronavirus – contact

Arabisch:

Allgemein

Schutzmaßnahmen gegen das Coronavirus – Atemhygiene

Schutzmaßnahmen gegen das Coronavirus – Augen, Nase, Mund

Schutzmaßnahmen gegen das Coronavirus – Distanz

Schutzmaßnahmen gegen das Coronavirus – Hände

Farsi:

Allgemein

Schutzmaßnahmen gegen das Coronavirus – Atemhygiene

Schutzmaßnahmen gegen das Coronavirus – Augen, Nase, Mund

Schutzmaßnahmen gegen das Coronavirus – Distanz

Schutzmaßnahmen gegen das Coronavirus – Hände

Türkisch:

Allgemein

Schutzmaßnahmen gegen das Coronavirus – Atemhygiene

Schutzmaßnahmen gegen das Coronavirus – Augen, Nase, Mund

Schutzmaßnahmen gegen das Coronavirus – Distanz

Schutzmaßnahmen gegen das Coronavirus – Hände

Serbisch, Kroatisch, Bosnisch:

Allgemein

Schutzmaßnahmen gegen das Coronavirus – Atemhygiene

Schutzmaßnahmen gegen das Coronavirus – Augen, Nase, Mund

Schutzmaßnahmen gegen das Coronavirus – Distanz

Schutzmaßnahmen gegen das Coronavirus – Hände

Für Kinder:

Was Kinder gegen COVID-19 tun können

Mehrsprachige Versionen

Schwerpunkt: Onkologie

Neue Behandlungsstandards beim Ovarialkarzinom: Starke Innsbrucker Beteiligung an 2 Studien

Publikationen im "New England Journal of Medicine" und "Lancet Oncology"

„Wie kürzlich im New England Journal of Medicine publiziert, verlängerte Lynparza das progressionsfreie Überleben von 16,6 auf 22,1 Monate."

Die Erstlinien-Chemotherapie beim Ovarialkarzinom im FIGO Stadium III und IV war bisher Carboplatin, Paclitaxel und Bevacizumab (Avastin). In der randomisierten PAOLA-1 Studie erhielten die Patientinnen aber neben der Chemotherapie auch den PARP-Inhibitor Olaparib (Lynparza) oder ein Placebo. Wie kürzlich im *New England Journal of Medicine* publiziert, verlängerte Lynparza das progressionsfreie Überleben von 16,6 auf 22,1 Monate. Dieser Effekt war am eindrucksvollsten bei Vorliegen einer somatischen Mutation im BRCA1oder BRCA2 Gen (medianes progressionsfreies Überleben wurde von 21,7 auf 37,2 Monate verlängert). Müdigkeit, Übelkeit und Anämie wurden durch den PARP-Inhibitor verstärkt, aber die Behandlung war insgesamt gut verträglich. Regina Berger, die Leiterin der an der Innsbrucker Frauenklinik ansässigen AGO-Studienzentrale, war Mitautorin der vielbeachteten Veröffentlichung, die nach der für den Herbst erwarteten Zulassung einen neuen Behandlungsstandard festlegen wird.

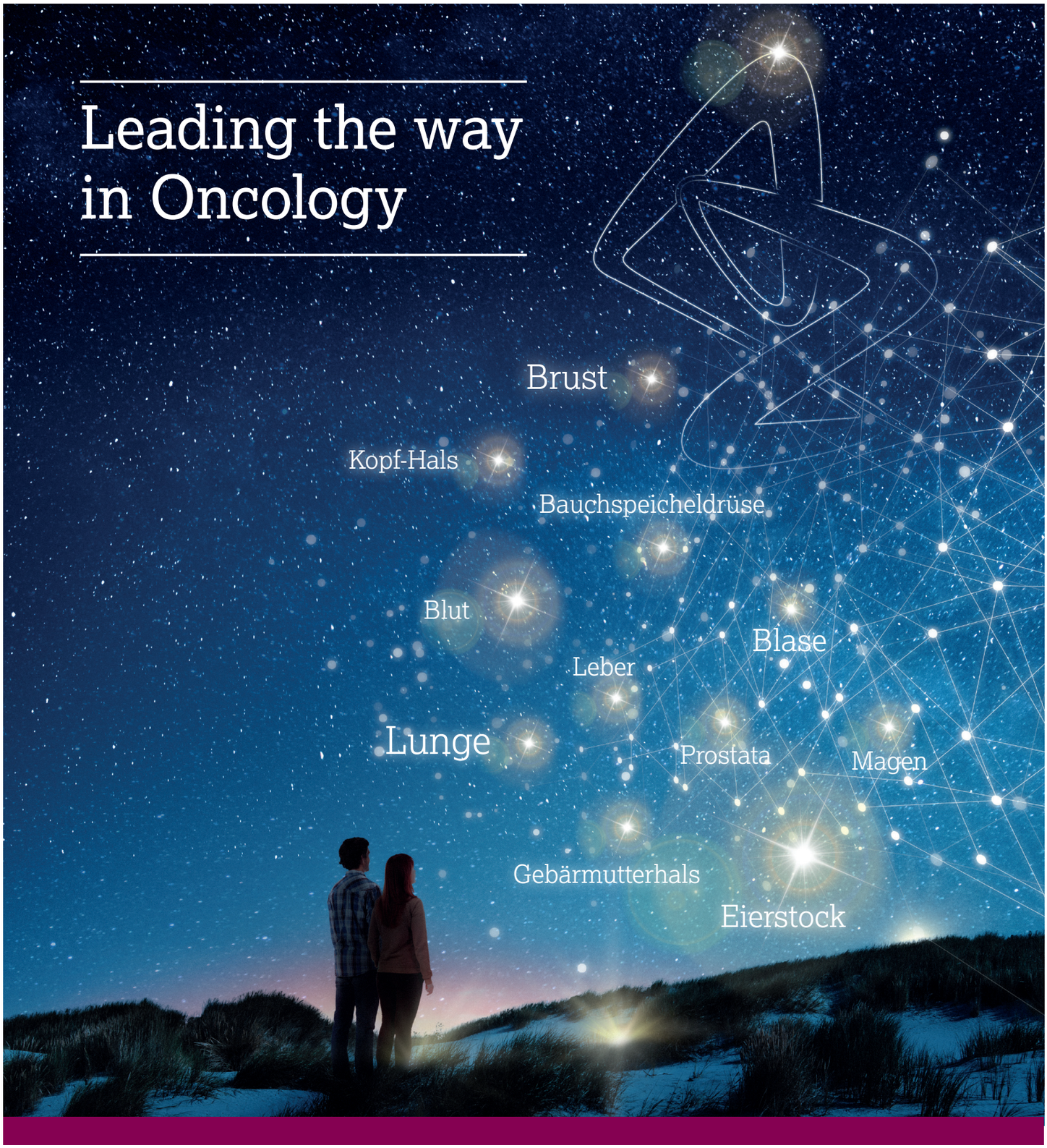
Bei sogenannten „platin-sensitiven" Rückfällen des Ovarialkarzinoms bestand die bisherige Behandlung zumeist aus Carboplatin, Gemcitabine und Bevacizumab (Avastin). Diese Therapie ist aber leider schlecht verträglich. Im Rahmen der AGO-OVAR 2.21 Studie wurde diese Behandlung mit Carboplatin, pegyliertem liposomalem Doxorubicin (Caelyx) und Bevacizumab verglichen. Diese experimentelle Behandlung verlängerte, wie vor wenigen Tagen im Fachblatt *Lancet Oncology* veröffentlicht, das progressionsfreie Überleben signifikant. Auch das Gesamtüberleben konnte durch diese neue Behandlungsform verlängert werden. Wichtig ist, dass die experimentelle Therapie nicht nur wirksamer, sondern auch besser verträglich ist. Für die Innsbrucker Klinik war Alain Zeimet Mitautor dieser bereits vielbeachteten und mit einem Editorial gewürdigten Veröffentlichung. An der Innsbrucker Klinik wurde diese Behandlung schon vor längerer Zeit als Standard eingeführt. Damit beweisen wir wieder einmal, dass Beteiligung an Studien Patientinnen einen frühen Zugang zur besten Medizin ermöglicht.

Mehr Details und Sonderdrucke können Sie bei den jeweiligen Autoren regina.berger@i-med.ac.at und alain.zeimet@i-med.ac.at erhalten.

Impressum

AutorInnen dieser Ausgabe: K. Kropshofer, MSc, Univ. Prof. Dr. C. Marth; Redaktionsteam: OÄ Dr.in S. Abdel Azim, OÄ Dr.in C. Brunner, OA Dr. D. Egle, Dr.in J. Kögl, K. Kropshofer MSc (Redaktion), OA Dr. S. Kropshofer, Univ. Prof. Dr. C. Marth (Klinikleitung), Mag. F. Preishuber (Klinikmanager), OÄ Dr.in A. Ramoni, I. Zeimet-Kirchmair (Lektorat)

AstraZeneca



AT-3275 / 03-2020

AstraZeneca forscht für eine lebenswertere Zukunft!

Die Grenzen der Wissenschaft erweitern – das volle Potenzial der Präzisionsmedizin erschließen: unsere Mission für PatientInnen.

www.astrazeneca.at

HOW TO WEAR A MEDICAL MASK SAFELY

who.int/epi-win

Do's

Wash your hands before touching the mask

Inspect the mask for tears or holes

Find the top side, where the metal piece or stiff edge is

Ensure the colored-side faces outwards

Place the metal piece or stiff edge over your nose

Cover your mouth, nose, and chin

Adjust the mask to your face without leaving gaps on the sides

Avoid touching the mask

Remove the mask from behind the ears or head

Keep the mask away from you and surfaces while removing it

Discard the mask immediately after use preferably into a closed bin

Wash your hands after discarding the mask

Don'ts

Do not Use a ripped or damp mask

Do not wear the mask only over mouth or nose

Do not wear a loose mask

Do not touch the front of the mask

Do not remove the mask to talk to someone or do other things that would require touching the mask

Do not leave your used mask within the reach of others

Do not re-use the mask

Remember that masks alone cannot protect you from COVID-19. Maintain at least 1 metre distance from others and wash your hands frequently and thoroughly, even while wearing a mask.

EPI·WiN World Health Organization

CORRESPONDENCE

Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China

TO THE EDITOR: Despite the large and rapidly rising number of cases of coronavirus disease 2019 (Covid-19) and resulting deaths,[1] there are limited data about the clinical characteristics of pregnant women with the disease.[2,3] We extracted information regarding epidemiologic, clinical, laboratory, and radiologic characteristics, treatment, and outcomes of pregnant women with Covid-19 through the epidemic reporting system of the National Health Commission of China, which stores the medical records of all 50 designated hospitals in Wuhan city.

From December 8, 2019, to March 20, 2020, we identified 118 pregnant women with Covid-19 in Wuhan according to the criteria of the Chinese Clinical Guidance for Covid-19 Pneumonia Diagnosis and Treatment; 84 women (71%) had positive polymerase-chain-reaction (PCR) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the remaining 34 (29%) had suggestive findings on computed tomography (CT) of the chest. Criteria for mild, severe, and critical disease and other methodologic details are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org. The pregnant patients represented 0.24% of all reported patients with Covid-19 at these hospitals during this time.

The median age of the women was 31 years (interquartile range, 28 to 34); 55 of 106 (52%) were nulliparous, and 75 of 118 (64%) had been infected with SARS-CoV-2 in the third trimester. The most common symptoms in 112 women with available data were fever (in 75%) and cough (in 73%) (Table 1). Lymphopenia was present in 51 of 116 patients (44%). A total of 88 of the 111 women (79%) who underwent chest CT had infiltrates in both lungs. Additional clinical data are provided in the Supplementary Appendix.

A total of 109 of 118 women (92%) had mild disease, and 9 (8%) had severe disease (hypoxemia), 1 of whom received noninvasive mechanical ventilation (critical disease). Severe disease developed in 6 of the 9 women after delivery, and the woman who received noninvasive mechanical ventilation did so after delivery. As of March 20, a total of 109 of 116 women (94%) had been discharged, including all women with severe or critical disease. There were no deaths.

Among the study population, there were 3 spontaneous abortions, 2 ectopic pregnancies, and 4 induced abortions (all owing to patients' concerns about Covid-19). A total of 68 of 118 patients (58%) delivered during the study period, accounting for 0.56% of all deliveries in Wuhan during this time, and had 70 births (2 sets of twins). Of these 68 patients, 63 (93%) underwent a cesarean section; in 38 of 62 cases (61%), the procedure was performed because of concern about the effects of Covid-19 on the pregnancy. A total of 14 deliveries (21%) were premature; 8 were induced (7 owing to concern about Covid-19). No babies had neonatal asphyxia.

Testing for SARS-CoV-2 was performed on neonatal throat swabs of 8 newborns and breast-milk samples of 3 mothers. No positive results were reported.

The risk of severe disease in our pregnant population (8%) compared favorably with the risk reported in the general population of patients presenting with Covid-19 across mainland China (15.7%).[4] Previous data have shown lower rates of severe disease among women and younger patients than among men and older patients.[4] The present data do not suggest an increased risk of severe disease among pregnant women, as has been observed with influenza.[5] The exacerbations of respiratory disease that are observed in women

Table 1. Demographic and Clinical Characteristics of Pregnant Women with Covid-19, According to Disease Severity.*

Characteristic	All Patients (N=118)	Disease Severity	
		Nonsevere (N=109)	Severe (N=9)
General characteristics			
Median age (IQR) — yr	31 (28–34)	30 (28–34)	34 (33–35)
Nulliparous — no./total no. (%)	55/106 (52)	51/97 (53)	4/9 (44)
Parous — no./total no. (%)	51/106 (48)	46/97 (47)	5/9 (56)
Signs and symptoms			
Asymptomatic — no. (%)†	6 (5)	6 (6)	0
Symptomatic — no. (%)‡	112 (95)	103 (94)	9 (100)
Fever — no./total no. (%)	84/112 (75)	77/103 (75)	7/9 (78)
Cough — no./total no. (%)	82/112 (73)	73/103 (71)	9/9 (100)
Chest tightness — no./total no. (%)	20/112 (18)	15/103 (15)	5/9 (56)
Fatigue — no./total no. (%)	19/112 (17)	17/103 (17)	2/9 (22)
Dyspnea — no./total no. (%)	8/112 (7)	5/103 (5)	3/9 (33)
Diarrhea — no./total no. (%)	8/112 (7)	6/103 (6)	2/9 (22)
Headache — no./total no. (%)	7/112 (6)	5/103 (5)	2/9 (22)
Pregnancy outcome			
Delivery — no. (%)	68 (58)	61 (56)	7 (78)
Live birth — no./total no. (%)§	70/70 (100)	63/63 (100)	7/7 (100)
Preterm birth — no./total no. (%)	14/68 (21)	11/61 (18)	3/7 (43)
Iatrogenic	8/14 (57)	6/11 (55)	2/3 (67)
Abortion — no. (%)	9 (8)	9 (8)	0
Spontaneous abortion — no./total no. (%)	3/9 (33)	3/9 (33)	0
Induced abortion — no./total no. (%)¶	4/9 (44)	4/9 (44)	0
Ectopic pregnancy — no./total no. (%)	2/9 (22)	2/9 (22)	0
Cesarean section — no./total no. (%)	63/68 (93)	58/61 (95)	5/7 (71)
Due to obstetrical indications	24/62 (39)	22/57 (39)	2/5 (40)
Due to concern about Covid-19	38/62 (61)	35/57 (61)	3/5 (60)
Natural delivery — no./total no. (%)	5/68 (7)	3/61 (5)	2/7 (29)
Pregnancy ongoing — no. (%)‖	41 (35)	39 (36)	2 (22)
Median 1-min Apgar score (IQR)**	9 (8–9)	9 (8–9)	8 (8–10)
Neonatal asphyxia — no./total no.	0/70	0/63	0/7
Neonatal death — no./total no.	0/70	0/63	0/7

* The denominators of patients who were included in each analysis are provided if they differed from the total numbers in the relevant study group. Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, and IQR interquartile range.
† Asymptomatic patients were screened because of exposure to persons with confirmed or suspected Covid-19.
‡ The signs and symptoms listed include those reported to occur before admission and during hospitalization. Data were extracted from the medical record and may not reflect complete accounting of symptoms.
§ The reason that there were 70 live births but 68 deliveries was that there were 2 sets of twins.
¶ These abortions were induced because of the patient's concern about Covid-19.
‖ The data shown are as of March 20, 2020.
** The Apgar score at 1 minute was available for 66 babies.

during the postpartum period are likely to relate to pathophysiological changes (e.g., increased circulating blood volume) that occur in this period.

Lian Chen, M.D.
Qin Li, Ph.D.
Danni Zheng, M.Med.Sc.
Hai Jiang, M.Med.Sc.
Yuan Wei, M.D.
Peking University Third Hospital
Beijing, China

Li Zou, M.D., Ph.D.
Union Hospital
Wuhan, China

Ling Feng, M.D., Ph.D.
Tongji Hospital
Wuhan, China

Guoping Xiong, M.D., Ph.D.
Central Hospital of Wuhan
Wuhan, China

Guoqiang Sun, M.Med.
Maternal and Child Hospital of Hubei Province
Wuhan, China

Haibo Wang, M.B., B.S., M.P.H.
First Affiliated Hospital of Sun Yat-sen University
Guangzhou, China

Yangyu Zhao, M.D., Ph.D.
Jie Qiao, M.D., Ph.D.
Peking University Third Hospital
Beijing, China
zhaoyangyu@bjmu.edu.cn
jie.qiao@263.net

Drs. Chen and Li, Ms. Zheng, and Mr. Jiang and Drs. Zhao and Qiao contributed equally to this letter.

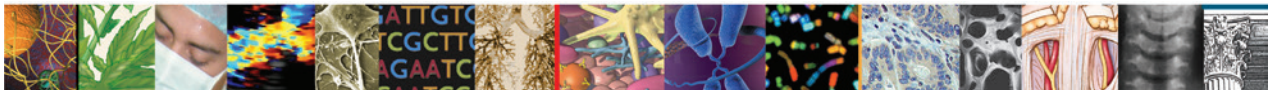
Supported by grants (72042013, 81521002, and 81730038) from the National Natural Science Foundation of China. The foundation had no role in the study design, the data analysis, the drafting of this letter, or the decision to submit it for publication.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on April 17, 2020, at NEJM.org.

1. World Health Organization. Coronavirus (COVID-19). 2020 (https://who.sprinklr.com).
2. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020;395:809-15.
3. Yu N, Li W, Kang Q, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis 2020 March 24 (Epub ahead of print).
4. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. DOI: 10.1056/NEJMoa2002032.
5. Creanga AA, Kamimoto L, Newsome K, et al. Seasonal and 2009 pandemic influenza A (H1N1) virus infection during pregnancy: a population-based study of hospitalized cases. Am J Obstet Gynecol 2011;204:Suppl 1:S38-S45.

DOI: 10.1056/NEJMc2009226



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Developing Covid-19 Vaccines at Pandemic Speed

Nicole Lurie, M.D., M.S.P.H., Melanie Saville, M.D., Richard Hatchett, M.D., and Jane Halton, A.O., P.S.M.

The need to rapidly develop a vaccine against SARS-CoV-2 comes at a time of explosion in basic scientific understanding, including in areas such as genomics and structural biology, that is supporting a new era in vaccine development. Over the past decade, the scientific community and the vaccine industry have been asked to respond urgently to epidemics of H1N1 influenza, Ebola, Zika, and now SARS-CoV-2. An H1N1 influenza vaccine was developed relatively rapidly, largely because influenza-vaccine technology was well developed and key regulators had previously decided that vaccines made using egg- and cell-based platforms could be licensed under the rules used for a strain change. Although a monovalent H1N1 vaccine was not available before the pandemic peaked in the Northern Hemisphere, it was available soon afterward as a stand-alone vaccine and was ultimately incorporated into commercially available seasonal influenza vaccines.

Vaccines for the severe acute respiratory syndrome (SARS), Ebola, and Zika did not follow a similar path. The SARS and Zika epidemics ended before vaccine development was complete, and federal funding agencies reallocated funds that had been committed to vaccine development, leaving manufacturers with financial losses and setting back other vaccine-development programs.

Development of an Ebola vaccine by the Public Health Agency of Canada had been on hold when the 2013–2016 Ebola outbreak began. The U.S. government provided funding to accelerate the vaccine's development, which was ultimately transferred to Merck. The company continued development even when the outbreak ended, and stockpiles of investigational product were available for use in the recent outbreaks in the Democratic Republic of Congo. The vaccine received conditional marketing authorization from the European Medicines Authority and approval from the U.S. Food and Drug Administration at the end of 2019 and in several African countries thereafter. Some companies working on Ebola vaccines have received external support and invested their own funds to continue development. Even with successful development and licensure, however, the prospect that commercial markets will sustain multiple vaccines for which relatively few doses may need to be manufactured seems dim.

Reviews of the experience with H1N1 vaccine have stressed the need for novel development-and-manufacturing platforms that can be readily adapted to new pathogens. Vaccine and biotech companies have been investing heavily in such approaches, with support from the U.S. government and other funders. The National Institute of Allergy and Infectious

Diseases has led an initiative to support early development of platforms and test them against "prototype pathogens" from various viral families.[1]

Our organization, the Coalition for Epidemic Preparedness Innovation (CEPI), an international nongovernmental organization funded by the Wellcome Trust, the Bill and Melinda Gates Foundation, the European Commission, and eight countries (Australia, Belgium, Canada, Ethiopia, Germany, Japan, Norway, and the United Kingdom), is supporting development of vaccines against five epidemic pathogens on the World Health Organization (WHO) priority list. We aim to develop reserves of investigational vaccines for each pathogen after such vaccines have completed phase 2a trials, expecting that they will undergo clinical trials during future outbreaks. CEPI also supports development of platform technologies to prepare for "Disease X" — a newly emerging epidemic disease, such as Covid-19. An ideal platform would support development from viral sequencing to clinical trials in less than 16 weeks, demonstrate elicitation of consistent immune responses across pathogens, and be suitable for large-scale manufacturing using a pathogen-agnostic platform.

Multiple platforms are under development. Among those with the greatest potential for speed are DNA- and RNA-based platforms, followed by those for developing recombinant-subunit vaccines. RNA and DNA vaccines can be made quickly because they require no culture or fermentation, instead using synthetic processes. Developers' and regulators' experience with these platforms for personal oncology vaccines can facilitate rapid testing and release. There are no approved RNA vaccines to date, but RNA vaccines have entered clinical trials, and regulators have experience in reviewing clinical trial applications and with associated manufacturing of the vaccines.

Use of next-generation sequencing and reverse genetics may also cut development time of more conventional vaccines during epidemics. The table lists major platform types and examples of SARS-CoV-2 vaccine types being developed on each. A more complete and continually updated list is available from the WHO.[2]

Even with novel platforms, SARS-CoV-2 vaccine development poses challenges. First, although the virus's spike protein is a promising immunogen for protection, optimizing antigen design is critical to ensure optimal immune response. Debate continues over the best approach — for example, targeting the full-length protein or only the receptor-binding domain.

Second, preclinical experience with vaccine candidates for SARS and the Middle East respiratory syndrome (MERS) have raised concerns about exacerbating lung disease, either directly or as a result of antibody-dependent enhancement. Such an adverse effect may be associated with a type 2 helper T-cell (Th2) response. Hence, testing in a suitable animal model and rigorous safety monitoring in clinical trials will be critical. (It is still too early to define good animal models; rhesus macaques appear quite promising, as do hamsters and ferrets [unpublished data].) If adjuvants are required to generate a sufficient immune response or for dose sparing, those triggering a Th1 response and demonstrating a high neutralizing-antibody response are theoretically more likely to be protective and avoid the risk of immunopathology. However, data and careful regulatory review will be needed.

Third, although correlates of protection may be inferred from experience with SARS and MERS vaccines, they are not yet established. As with naturally acquired infection, the potential duration of immunity is unknown; similarly, whether single-dose vaccines will confer immunity is uncertain.

Vaccine development is a lengthy, expensive process. Attrition is high, and it typically takes multiple candidates and many years to produce a licensed vaccine.[3] Because of the cost and high failure rates, developers typically follow a linear sequence of steps, with multiple pauses for data analysis or manufacturing-process checks. Developing a vaccine quickly requires a new pandemic paradigm (see diagram), with a fast start and many steps executed in parallel before confirming a successful outcome of another step, hence resulting in elevated financial risk. For example, for platforms with experience in humans, phase 1 clinical trials may be able to proceed in parallel with testing in animal models.

As soon as China announced that a novel coronavirus had been identified as the cause of the Wuhan outbreak, CEPI contacted its partners that were developing MERS vaccines or working on novel platforms. With the potential for further financial support, they and others began vaccine development as soon as the first gene sequence was posted, and development is proceeding quickly. Moderna's mRNA-based SARS-

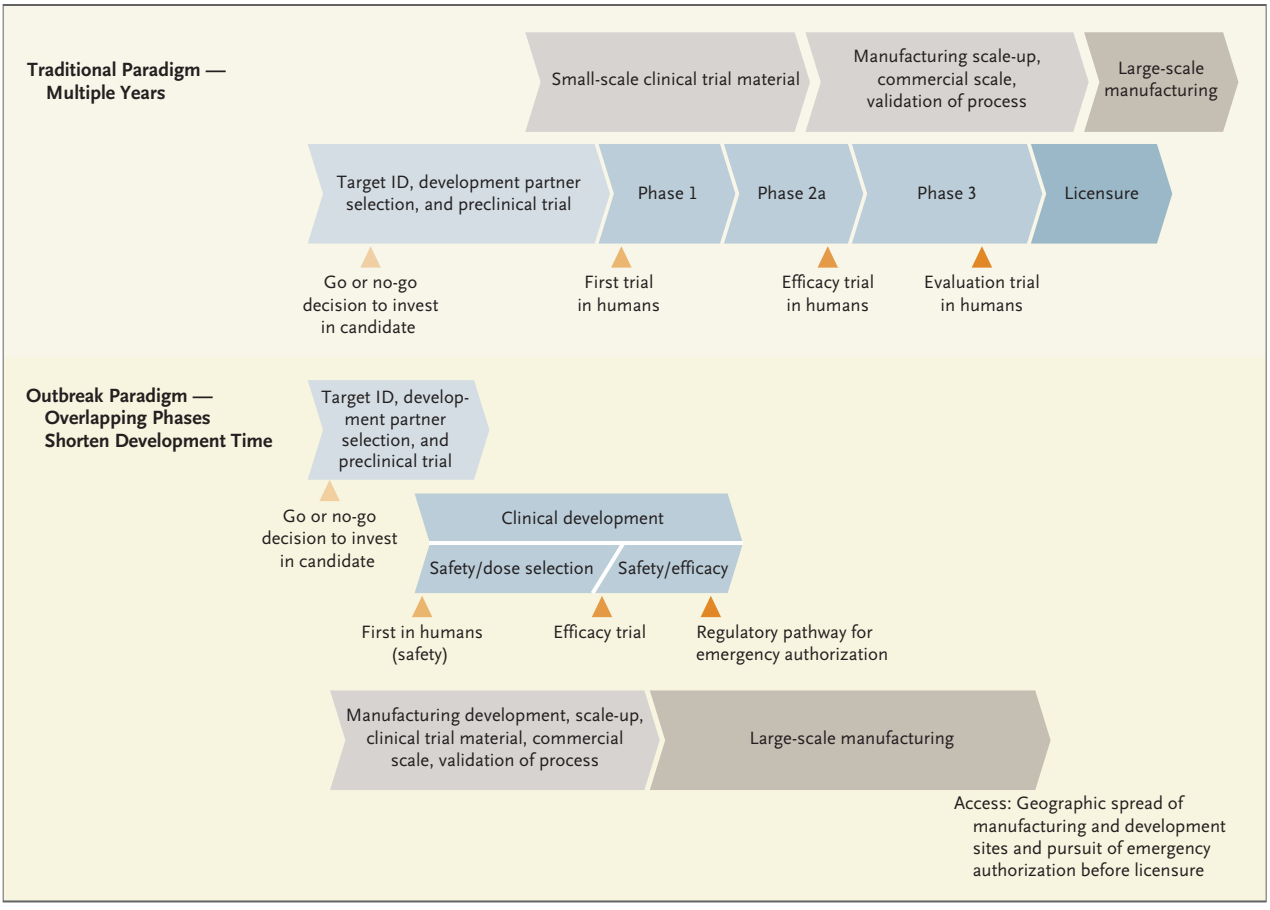
Vaccine Platforms, Their Attributes, and the Status of Vaccine Candidates.*

Technology	Attributes				Candidates in Preclinical Development	Candidates in Phase I
	Single Dose	Licensed Platform	Speed	Current Scale		
DNA	No	No	Fast	Medium	Inovio Pharmaceuticals Takis/Applied DNA Sciences/Evvivax Zydus Cadila	
Inactivated	No	Yes	Medium	Medium to high	Sinovac	
Live attenuated	Yes	Yes	Slow	High	Codagenix/Serum Institute of India	
Nonreplicating vector	Yes	No	Medium	High	GeoVax/BravoVax Janssen Pharmaceutical Companies University of Oxford Altimmune Greffex Vaxart ExpresS2ion	CanSino Biologics (ChiCTR20000 30906)
Protein subunit	No	Yes	Medium to fast	High	WRAIR/U.S. Army Medical Research Institute of Infectious Diseases Clover Biopharmaceuticals Inc/GSK Vaxil Bio AJ Vaccines Genrex/EpiVax/University of Georgia Sanofi Pasteur Novavax Heat Biologics/University of Miami University of Queensland/GSK/ Baylor College of Medicine iBio/CC-Pharming	
Replicating viral vector	Yes	Yes	Medium	High	Zydus Cadila Institut Pasteur/Themis Tonix Pharma/Southern Research	
RNA	No	No	Fast	Low to medium	Fudan University/Shanghai JiaoTong University/RNACure Biopharma China CDC/Tongji University/Stermina Arcturus/Duke-NUS Imperial College London Curevac BioNTech/Pfizer	Moderna/NIAID (NCT04283461)
Uncertain					University of Pittsburgh University of Saskatchewan ImmunoPrecise MIGAL Galilee Research Institute Doherty Institute Tulane University	

* Attributes refer to general attributes of the platform, and assessments are not intended as inferences about a particular candidate. NIAID denotes National Institute of Allergy and Infectious Diseases, and WRAIR Walter Reed Army Institute of Research.

CoV-2 candidate entered a phase 1 clinical trial on March 16, less than 10 weeks after the first genetic sequences were released; the first phase 1 trial with a nonreplicating vector-based vaccine has regulatory clearance to start phase 1 studies in China. Other phase 1 trials of nucleic acid vaccines are expected to start in April.

For some candidates, additional clinical trial material for phase 2 studies is being manufactured now; proceeding rapidly beyond phase 2 trials means manufacturing will need to be scaled up to commercial levels before substantial safety and immunogenicity data are available. Building manufacturing capacity can cost hundreds of millions of dollars. Furthermore, for novel platform technologies, most of which are unlicensed, large-scale manufacturing has never been done, so facilities capable of producing large quantities of product must be identified, technologies transferred, and manufacturing processes adapted, all without know-



Difference between Traditional Vaccine Development and Development Using a Pandemic Paradigm.

The pandemic paradigm requires multiple activities to be conducted at financial risk to developers and manufacturers and without knowing whether the vaccine candidate will be safe and effective, including very early manufacturing scale-up to commercial scale before establishment of clinical proof of concept. ID denotes identification.

ing if the vaccine candidate is viable.

It's far from certain that these new platforms will be scalable or that existing capacity can produce sufficient quantities of vaccine fast enough. It's therefore critical that vaccines also be developed using tried-and-true methods, even if they may take longer to enter clinical trials or to result in large numbers of doses.

Conducting clinical trials during a pandemic poses additional challenges. It's difficult to predict where and when outbreaks will occur and to prepare trial sites to coincide with vaccine readiness for testing. In addition, if multiple vaccines are ready for testing in the second half of 2020, it will be important not to crowd sites or burden countries and their ethics and regulatory authorities with multiple trials, as happened with Ebola therapeutics during the 2013–2016 outbreak.

Moreover, in a high-mortality situation, populations may not accept randomized, controlled trials with placebo groups; although other approaches that address such concerns may be scientifically feasible, they're typically not as fast, and the results can be harder to interpret.[4] This problem can sometimes be overcome by comparing outcomes with early vaccination versus delayed vaccination, as in the "Ebola ça suffit!" trial. One possible way forward would be to test several vaccines simultaneously in an adaptive trial design using a single, shared control group, so that more participants would receive an active vaccine.[5] This approach has advantages but can be logistically and statistically complex, and developers often avoid trials that may generate head-to-head comparative data.

CEPI, as a relatively new organization, had not established financial mechanisms and instruments to support development of

pandemic vaccines and will need to raise additional funds to see SARS-CoV-2 vaccines through the development and scale-up manufacturing processes. Although as many as several million vaccine doses may become available as a by-product of development, in a pandemic situation, once vaccine candidates are proved safe and effective, doses must be manufactured in large quantities. Though some high-income countries may pay for development and manufacture with their own populations in mind, there's no global entity responsible for financing or ordering vaccine manufacture. Discussions with global stakeholders about organizing and financing large-scale vaccine manufacturing, procurement, and delivery are under way.

Finally, pandemics will generate simultaneous demand for vaccines around the world. Clinical and serologic studies will be needed to confirm which populations remain at highest risk once vaccines are available and could form the basis for establishing a globally fair vaccine-allocation system. Some Group of Seven countries have already called for such a global system, whose planning must start while vaccine development proceeds.

Though it's unlikely, if the pandemic appears to abruptly end before vaccines are ready, we should continue developing the most promising candidates to a point at which they can be stockpiled and ready for trials and emergency authorization should an outbreak recur. A global financing system that supports end-to-end development and large-scale manufacturing and deployment, ensures fair allocation, and protects private-sector partners from significant financial losses will be a critical component of future pandemic preparedness.

Disclosure forms provided by the authors are available at NEJM.org.

From the Coalition for Epidemic Preparedness Innovations, Oslo.

This article was published on March 30, 2020, at NEJM.org.

1. Marston HD, Paules CI, Fauci AS. The critical role of biomedical research in pandemic preparedness. JAMA 2017;318:1757-8.
2. World Health Organization. Draft landscape of Covid-19 candidate vaccines. March 20, 2020 (https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus-landscape-ncov.pdf?ua=1).
3. Gouglas D, Thanh Le T, Henderson K, et al. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. Lancet Glob Health 2018;6(12):e1386-e1396.
4. National Academies of Sciences, Engineering, and Medicine. Integrating clinical research into epidemic response: the Ebola experience. Washington, DC: National Academies Press, 2017.
5. World Health Organization. A coordinated global research roadmap. 2020 (https://www.who.int/blueprint/priority-diseases/key-action/Roadmap-version-FINAL-for-WEB.pdf?ua=1).

DOI: 10.1056/NEJMp2005630