DIA 17. MESA I. Diagnóstico de laboratorio en la COVID-19

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SARS-COV-2 Variants: Clinical and Epidemiological Implications

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SARS-CoV-2 has been continuously evolving since it first reached humans in December 2019, and will continue to do so, unless virus replication and onward transmissions are completely halted. Already in January 2020, a variant including the D614G mutation in the spike domain emerged in Europe and the US. It rapidly substituted the ancestral Wuhan strain, becoming the predominant variant around the world by March 2020. This initial mutation conferred 20% increased transmissibility to the new variant relative to its antecessor. Studies, however, did not firmly identify an increased ability of D614G to avoid neutralizing antibody responses or lead to worse clinical outcomes. Other demographic and clinical factors such as age, body mass index and comorbidities were better determinants of clinical complications. After the D614G mutant, other variants have continued to emerge, each one substituting its antecessor.

Until late 2020, SARS-CoV-2 was evolving at a relatively slow pace globally. Coronaviruses mutate more slowly than most other RNA viruses, because they have a 'proofreading' enzyme that corrects potentially fatal copying mistakes. Indeed, a typical SARS-CoV-2 virus accumulates only two single-letter mutations per month in its genome —a rate of change about half that of influenza and one-quarter that of HIV-1. Two SARS-CoV-2 viruses collected from anywhere in the world differ by an average of just 10 RNA letters out of approximately 30000.

However, by December 2020 three new SARS-CoV-2 variants (B.1.1.7, B.1.351 and P1) carrying an unusually high number of mutations in different virus domains including the spike were identified. Such mutations either conferred increased transmissibility, allowed them to partially evade neutralizing responses, or completely evade the effect of some therapeutic monoclonal antibodies. (Table 1) The emergence of the three variants was associated with increases in hospitalizations and deaths in the places where they emerged. This prompted to a renewed interest in molecular epidemiology surveillance of SARS-CoV-2 around the World.

There are thousands of variants coexisting simultaneously in our Planet, but only those better able to replicate and outcompete the pre-existing ones predominate. Such advantage may arise because variants incorporate mutations that either increase intrinsically their replicative capacity (e.g. increase ACE2 receptor binding), or confer them a selective advantage against natural or vaccine-induced immune responses. To date, no new variant has been associated with increased lethality. However, the emergence of a more transmissible variant, in the absence of an adequate population vaccine coverage or social distancing measures, may lead to exponential increases in COVID-19 cases, hospitalizations and deaths, which may be remarkably higher than with just a more lethal variant.

The good news is that, so far, none of such variants have been associated with reduced vaccine effectiveness in terms deaths and severe illness. Thus, as the SARS-CoV-2 vaccination campaigns progress in rich countries, the clinical and epidemiological impact

Table. Features of the main variants of concern, by June 2021

	New WHO name	First Identified	Transmissibility	Immune evasiveness	mAb resistance	Vaccine effectiveness vs severe illness
Ancestral	-	Wuhan	-	-	-	✓
D614G	-	NA	+	-	-	✓
B.1.1.7	Alpha	Kent / UK	+++	-	-	✓
B.1.351	Beta	Brazil	+	++++	BAM and BAM+ETE	✓
P.1	Gamma	South Africa	++	++	BAM and BAM+ETE	✓
B.1.429	Epsilon	California	+	+	BAM	✓
B.1.526	Iota	New York	+	+	BAM	✓
B.1.617.2	Delta	India	++++	++	-	✓

Source: Eric Topol Twitter account @EricTopol; bamlanivimab (BAM); etesevimab (ETE).

of such variants is expected to be increasingly smaller and highly determined by vaccine coverage rates. Whereas the irruption of the B.1.7.7 variant in the UK on September 2020 in time of little social distancing measures and low vaccination rates led to an explosion of cases, hospitalizations and deaths; social distancing measures enforced in Spain when this variant entered in January 2021 likely prevented a similar burst in cases and deaths despite the B.1.7.7 substitution occurred as predicted. This shows that the clinical and epidemiological impact of novel variants depend not only on purely biological factors, but also on the social & economical context of the region where a new variant arises. This includes vaccination coverage rates and the ability and rapidity to enforce social distancing measures when needed.

The more recent B.1.617.2 ("Indian") variant led to a burst of cases, hospital admissions and deaths in the Indian continent. When this variant emerged, India had very low vaccine coverage and minimal (if any) social distancing measures in place. The emergence of the B.1.617.2 variant in the UK has found the country with >50% vaccination coverage, but with many social distancing measures lifted, and there is now uncertainty as to how will cases, hospitalizations and deaths evolve. The B.1.617.2 variant appears to be at least 50% more transmissible than B.1.7.7, and may partially evade humoral immune responses. As this report is being written, the UK is seeing an increase in community transmission and in number of cases although, so far, new cases mostly occur among young, unvaccinated or partially vaccinated subjects. It is too early to say whether or not, or for how long such trends will last, and how it will translate into hospitalizations, severity and mortality of the disease.

In summary, a number of variants of interest (VOI, for those with potential for increased transmission, immune evasiveness or lethality) and variants of concern (VOC, i.e., those with confirmed increased transmission or immune evasiveness, or both) will continue to affect humans until onward SARS-CoV-2 transmission is halted throughout the world. By definition, every new variant able to outcompete the former/s and become predominant in the population will be more transmissible and better adapted than the previous ones. Some of such new variants may no longer be treatable with some monoclonal antibodies or small molecules targeting the virus spike (Table). However, the real threat of the ongoing evolution and progressive adaptation of SARS-CoV-2 to human populations is the emergence of variants able to completely evade vaccine effectiveness and lead, again, to increased hospitalizations and deaths. This would require reengineering of the currently available vaccines, which is feasible, but would significantly complicate our ability to contain and control the SARS-CoV-2 pandemic. Having multiple vaccine versions would worsen vaccine shortages and lead to logistical obstacles difficult to surmount.

The only way to stop SARS-CoV-2 variant evolution, thus, is by halting onward transmissions. In turn, as of today, the only way of halting onward transmissions is to keep vaccinating everyone in the World as fast as possible with complete vaccine regimens. This has to include the poorest and most disenfranchised countries and populations in the world, which in the past, has proven to be extraordinarily difficult. New, cheap and available antivirals are urgently needed to aid in this effort, by enabling test-and-treat approaches, particularly in outbreaks. It is unknown what vaccine population coverage will be needed to protect us against incoming variants. Although relatively low vaccine coverages (30-50%) have already led to significant reductions in hospitalizations, ICU admissions or deaths, it is likely that much higher vaccine coverage (at least 70-80%) will be needed to effectively protect societies from incoming and emerging variants. An important caveat to keep in mind, is that increasing the selective pressure against a species without ending its ability to replicate

or transmit may, in fact, accelerate its evolution. Therefore, soft or medium-intensity interventions may be counterproductive in terms of variant evolution.

We must vaccinate everyone, but we must do it fast, and with complete, highly effective regimens. This may include adding boosting vaccine doses if needed. Until we are able to achieve complete virus control, we need novel antiviral test-and-treat approaches, and must keep on doing SARS-CoV-2 screens and apply social distancing measures when needed.

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Seroprevalencia de la infección por SARS-CoV-2 en España: Estudio ENE-COVID

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Introducción

El objetivo del Estudio Nacional sero-Epidemiológico de la infección por SARS-CoV-2 ENE-COVID fue caracterizar la difusión de la epidemia en nuestro país.

Desarrollo y resultados del estudio

ENE-COVID es un estudio longitudinal de base poblacional en el que los participantes fueron seleccionados mediante muestreo bietápico estratificado por provincia y tamaño municipal, seleccionando de forma aleatoria 1.500 secciones censales (1ª etapa) y 24 hogares (2ª etapa) en ellas. Todas las personas presentes en el hogar fueron invitadas a participar en las 4 rondas del estudio[1]. Se utilizaron dos tests de anticuerpos IgG complementarios, validados previamente. Un test rápido (digitopunción), que feacilita la participación y un inmunoensayo quimioluminiscente de micropartículas que requiere muestra de sangre y presenta mayor precisión[1].

Todos los análisis se realizan asignando a cada participante del estudio un peso de muestreo inversamente proporcional a su probabilidad de selección, ajustado también por la tasa de no respuesta específica según sexo, grupo de edad y nivel de renta relativo de la sección censal[1].

Las 3 primeras rondas del estudio, llevadas a cabo cada 3 semanas desde finales de abril a finales de junio de 2020, informan de la primera onda epidémica[1]. La seroprevalencia se situó en torno al 5%, con una gran heterogeneidad geográfica: mientras Ceuta, Murcia, Asturias, Galicia, Baleares y Canarias tenían prevalencias inferiores o cercanas al 2%, las Comunidades de Castilla-La Mancha y Madrid se aproximaban o superaban el 10%[1,2]. ENE-COVID proporcionó información de prevalencia de infección en todos los grupos de edad, desde bebés hasta nonagenarios, sin detectar grandes diferencias, salvo una menor prevalencia en niños y adolescentes[2], mientras que la imagen obtenida a través de los casos confirmados en ese momento parecía indicar mayores tasas de infección en los grupos de mayor edad[3]. ENE-COVID también mostró que SARS-CoV-2 infectaba por igual a hombres y mujeres[4], conclusión diferente a la obtenida con la información de casos confirmados. Nuestro estudio cuantificó también la proporción de infecciones asintomáticas, en torno al 30%[2]. Los

datos de seroprevalencia identificaron también el mayor riesgo de infección del personal sanitario[2] y de las personas que convivieron con pacientes COVID-19 o con personas con síntomas compatibles con esta enfermedad[2].

Combinando la información de ENE-COVID con los datos de mortalidad obtenidos en la Red Nacional de Vigilancia Epidemiológica y en el Sistema de Monitorización diaria de la Mortalidad (MoMo) hemos podido cuantificar la letalidad del SARS-CoV-2 en la población española no institucionalizada durante esta primera onda epidémica, situándose entre un 0,8% y un 1,1%, con grandes diferencias en función de la edad y el sexo[5].La mortalidad entre los infectados menores de 50 años fue escasa, mientras que fue superior al 10% en los hombres de 80 años y más y en torno al 5-6% en las mujeres del mismo grupo etario[5]. Estas cifras, como decimos, no reflejan lo ocurrido en las residencias de mayores.

La 4ª ronda (2ª quincena de noviembre) de ENE-COVID ha servido para caracterizar la segunda onda epidémica[1]. En esas fechas, uno de cada 10 españoles había sido infectado, mientras que en Madrid, Albacete, Cuenca y Soria la seroprevalencia global se aproximaba ya al 20%. Las diferencias geográficas, todavía muy patentes, se reducían como consecuencia de la penetración del virus en territorios apenas afectados durante la primera onda epidémica. Mientras que en dicha onda apenas se percibían diferencias según el nivel de renta, en la segunda onda epidémica esas diferencias comienzan a ser visibles[1].

Discusión y conclusiones

ENE-COVID ha servido para describir las dos primeras ondas epidémicas en nuestro país, proporcionando información de las dimensiones reales de la pandemia y las características sociodemográficas relacionadas con una mayor o menor probabilidad de infección.

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