Conceptual Analysis of COVID-19 in Phase 3 Clinical Trials: a Hierarchical

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ABSTRACT

The emergence of a novel SARS-CoV-2 coronavirus at the end of 2019 and its accelerated spread worldwide to become a pandemic has had, from the medical biotechnology point of view, an unprecedented global response, to the point that there are currently 176 vaccine candidates in the preclinical stage and 66 in clinical stage. The purpose of the present work is to elaborate a hierarchical landscape of the current status of 12 phase 3 vaccines, taking into account their attributes of technological platform, safety, and efficacy. The methodology used was that of conceptual knowledge representation, resulting in, firstly, appropriate classification of stage 3 vaccines, in four categories, the first made up of the BBIBP-CorV, BBV152, CoronoVac and Wuhan Institute vaccines; the second Medicago's CoVLP vaccine; the third, conformed by NVX-CoV2373, BNT162, AstraZeneca (AZD1222); and the fourth, conformed by Ad26.COV2. S and Ad5-nCoV. This hierarchy of COVID-19 vaccines enables the development of adaptable strategies to implement cost-effective clinical trials aimed at controlling the pandemic.

Keywords: SARS-CoV-2; COVID-19; Vaccines; Hierarchical analysis; Conceptual analysis

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to spread throughout the world with explosive outbreaks underway throughout much of Europe and the United States [1]. To control the disease, governments, international organizations, private companies, and academic institutions across the planet have launched a multifaceted vaccine development response with unprecedented rapidity. According to WHO [2,3], 176 vaccine candidates are in preclinical testing and at least 66 vaccines have already begun early clinical testing, and actually, at least 19 vaccines are in phase 3 clinical development, and 12 vaccines are authorized to be used worldwide [4]. These facts indicate that effective vaccines have been emphasized to become the most effective strategy in the global fight against the COVID-19 pandemic [5-7], and given the actual number of promising COVID-19 vaccine candidates, elaborated from diverse technological platforms, with a broad range of efficacy and immunogenicity results reported in those individuals who underwent clinical trials, it is very important to build a rational landscape of phase 3 COVID-19 vaccines [7].

This study aims to perform a comparative analysis of twelve clinical stage 3 COVID-19 vaccines building a hierarchical model of them, based on their attributes related to safety, efficacy, cost, dosing schedule, and technological platform. To meet the proposed objective, the Formal Concept Analysis (FCA) is used [9], this is a method for knowledge representation and information management that is widely known among information scientists all around the world because of its broad range of applications outside mathematics like economics, industry, chemistry, linguistics and environmental sciences among others [10-14].

It should be noted that although all the vaccines considered in the present study have shown that they induce a protective humoral immune response against SARS-CoV-2 and are safe, clear differences can be observed concerning the levels of neutralizing antibodies and the technological platform on which were made v.gr. DNA vaccines induce lower antibody titers in contrast to RNA vaccines, viral particles, and viral-like particles, which in general are strongly reactogenic and produce high levels of neutralizing IgG. non-replicating virus and inactivated virus vaccines induce medium to high antibody levels and exhibit less reactogenicity.

Finally taking into account cost and efficacy, it is important to note that the hierarchical structure that relates to the set of 12 vaccines considered, allows defining 4 categories, the first made up of the BBIBP-CorV, BBV152, CoronoVac, and Wuhan Institute vaccines; the second Medicago's CoVLP vaccine; the third, conformed by NVX-CoV2373, BNT162, AstraZeneca (AZD1222); and the fourth, conformed by Ad26.COV2. S and Ad5-nCoV. This classification allows establishing different vaccination strategies depending on the social and economic variables that characterize the population to be vaccinated.

CONCEPTUAL ANALYSIS

The rapid development of vaccines to control COVID-19 has been closely followed by various organizations around the world, for February 12, 2021, the World Health Organization [4] in its report Covid-19 Landscape of Novel Coronavirus Candidates Vaccines Development Worldwide lists a total of 176 vaccines in the preclinical stage, 66 in the clinical phase, of which 16 are in phase 3 clinical studies. Other entities such as the Milken Institute [15], report similar numbers, 248 vaccines in development, 56 are in the clinical phase, of which 12 are currently in use. On the other hand, various authors [5-7] report the technological, safety, and immunogenicity characteristics of each of phase 3 and/or authorized vaccines. Based on these reviews, Table 1 is organized, with a total of 12 vaccines in phase 3 and/or authorized, to carry out the present study.

Table 1: COVID-19 Vaccines in clinical phase 3 stage used for the present study. All these vaccines have shown efficacy in Phase 3 clinical trials through the induction of neutralizing IgG antibodies against SARS-CoV-2.

Producer	Type of candidate vaccine	Reference
Novavax	NVX-CoV2373	[17]
Beijing Institute of Biological Products	BBIBP-CorV	[18]
CanSino Biologics	Ad5-nCoV	[3,4,19]
Wuhan Institute of Biological Products	Novel CoV Pneumonia Vac	[20]
Janssen Pharmaceutical Companies	Ad26.COV2-S	[21]
Sinovac/ Instituto Butantan/ Bio Farma	CoronaVac (formerly PiCoVacc)	[22]
Gamaleya Research Institute	(Gam-COVID-Vac) (Sputnik V)	[23,24]
Bharat Biotech	(COVAXIN) (BBV152)	[25]
Moderna	(mRNA 1273), (TAK-919)	[26]
BioNTech/ Pfizer	BNT162	[27]
AstraZeneca	COVID-19 Vaccine AstraZeneca	[28,29]
Medicago Inc.	(CoVLP)	[3,4]

The conceptual analysis of COVID-19 vaccines in phase 3 clinical trials was performed using the theoretical framework of Formal Concept Analysis (FCA), a mathematical theory oriented, in particular, at applications in knowledge representation, knowledge acquisition, and data analysis. In [9] Ganter & Wille introduced Formal Concept Analysis as an application of order and lattice theory based on a set-theoretical model for conceptual hierarchies. This model mathematizes the philosophical understanding of a concept as a unit of thoughts consisting of two parts: the extension and the intension (comprehension). The extension covers all objects (or entities) belonging to the concept, while the intension comprises all attributes (or properties) valid for all the objects under consideration. The conceptual methodology was extensively explained in Burgos [10].

To construct the conceptual hierarchy, to each of the 12 vaccines listed in table 1, a total of 5 attributes were taken into account: the technological platform on which the vaccine was developed, the application scheme, the reactogenicity or percentage of incidence of adverse effects, the efficacy and finally, the cost per dose was considered an important attribute, since it can become a limitation for the massive use of a vaccine, taking into account that the insurance vaccination campaigns will last for several years and many of the patients will live in low-income countries or regions. The values assigned to each attribute correspond to those cited in the literature and are presented in Table 2.

Table 2: Attributes of phase 3 COVID-19 vaccines and its values. The values for efficacy and cost per dose were obtained from Collier et al. 2021 [30].

Attribute	Value
Technological Platform	Protein subunit; inactivated virus; mRNA; nonreplicating virus; viral like particle
Dosing schedule (days)	0; 0+14; 0+21; 0+28; 0+56
Safety (% of reactogenicity)	0-25; 26-50; 51-75; 76-100
Efficacy (%)	50-66; >66-85; >85
Cost (USD/dose)	2-10; >10-37; >37

RESULTS

The conceptual analysis indicates that there is a direct relationship between the reactogenicity of the vaccines and their ability to induce neutralizing IgG antibodies. The higher the incidence of adverse effects, the higher the antibody titers are obtained. of course, reactogenicity generally consists of minor discomforts such as redness, fever, pain, and others widely described elsewhere in the literature [8]. It should also be noted that the most effective dosage, regardless of the technological platform of the vaccine, is that of two doses delivered 21 days apart.

In particular, a possible strategy in countries with populations of older people and/or a high presence of comorbidities, the use of vaccines NVX-CoV2373, BNT162, MODERNA, Gam-COVID-VAC could be recommended (figure 2). It should be noted that RNA vaccines are also proving to be effective against new variants of the virus [31].

On the other hand, if the objective is that of rapid deployment, at low costs per dose, without making large investments in cold chain issues of minus 70 degrees Celsius, single-dose vaccines such as Ad26.COV2. S and Ad5-nCoV (figure 3) are certainly the ones of choice. These two vaccines can be very successful in

developing countries with predominantly young populations. Moreover, the conceptual hierarchy of the twelve vaccines represented in Figure 1, allows to establish, reading the lattice from bottom to top, a set of 4 categories, the first one is made up of the BBIBP-CorV, BBV152, CoronoVac, and Wuhan Institute vaccines, which are elaborated from Inactivated viruses have reactivity of up to 50% incidence, efficiencies between 50 and 85% and some have a cost per dose of USD 30 or more.
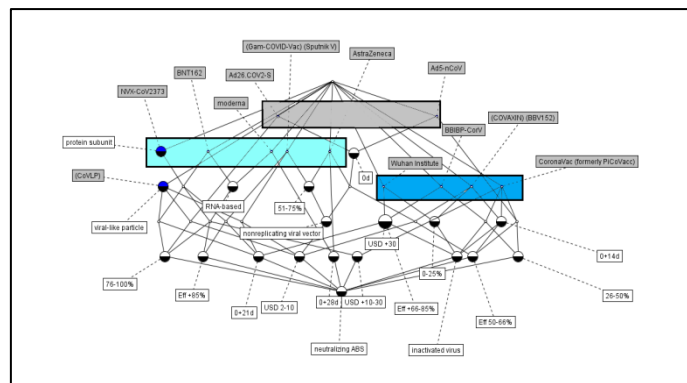

Figure 1: The COVID-19 Vaccine Conceptual Hierarchy. This lattice represents the four categories inside which the 12 vaccines can be arranged. From bottom to up, the first made up of the BBIBP-CorV, BBV152, CoronoVac and Wuhan Institute vaccines (blue rectangle); the second Medicago's CoVLP vaccine (blue/black circle); the third, conformed by NVX-CoV2373, BNT162 and AstraZeneca (AZD1222) (light blue rectangle); and the fourth, conformed by Ad26.COV2. S and Ad5-nCoV (grey rectangle).
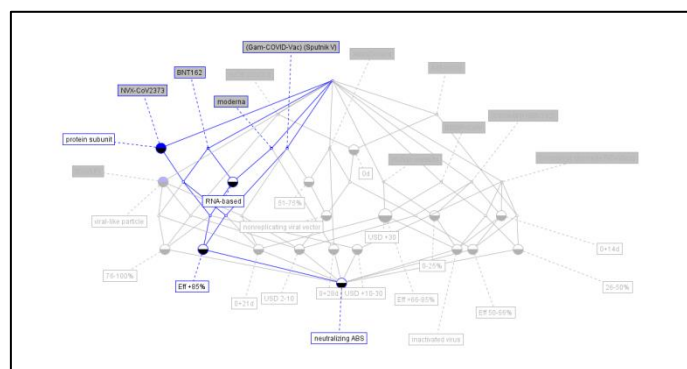

Figure 2: Conceptual lattice of NVX-CoV2373, BNT162,

MODERNA, Gam-COVID-VAC vaccines who belongs to the set of those ones with highest efficacy.
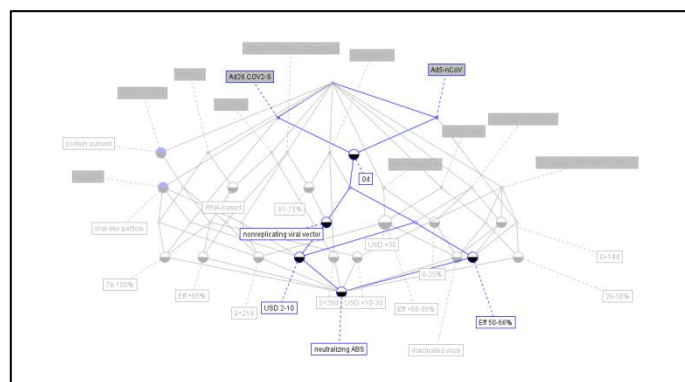

Figure 3: Conceptual lattice of Adenovirus based vaccines Ad26.COV2. S and Ad5-nCoV.

Second, there is Medicago's CoVLP vaccine, which is very promising for several reasons, its Nicotiana benthamiana cell culture platform can make it very cheap and scalable, and safe. The results of phase 1 and phase 2 clinical trials have shown that the vaccine induces high titers of neutralizing IgG antibodies against SARS-CoV-2. Once the results of phase 3 are known, they can be compared more adequately with relation to the other vaccines considered in the present study.

Thirdly, there are the vaccines NVX-CoV2373, BNT162, AstraZeneca (AZD1222), Moderna, and Sputnik V, which are characterized by their high reactogenicity, in the case of RNA vaccines, efficacy with levels of protection reported higher than 85%, and costs for doses less than 30 dollars. Fourth, there are two non-replicating virus vaccines Ad26.COV2. S and Ad5-nCoV, which are cheap (USD 2-10), are applied in a single dose and their efficacy is 50 to 66%.

The evidence provided by this research should be correctly contextualized and interpreted with caution, especially for the potential clinical implications, but what is clear is that, with the current hierarchy of vaccines for COVID-19 available, it is possible to develop strategies adaptable to the demographic and socio-cultural characteristics of a large part of the countries of the world, which are currently struggling to contain the pandemic and reestablish their economy.

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