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Short communication

Initiation of a coronavirus vaccine library

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ABSTRACT

Coronaviruses (CoVs) continue to pose a global health threat as they spill over from animal hosts to humans. The Coalition for Epidemic Preparedness Innovations (CEPI) is a global partnership focused on vaccine research and development. CEPI's CoV Vaccine Library initiative aims to generate knowledge and tools to accelerate vaccine development against emergent CoVs, prioritizing those with the highest assessed risk of spillover, vaccine feasibility, and phylogenetic coverage. Based on expert consultations and published data, we developed a prioritized list of 26 CoVs to serve as a foundation for building a knowledge base to support future vaccine efforts. As a first step, *in silico* designs will be used to develop stabilized spike antigens for select targets. These antigens will be tested for pre-clinical immunogenicity and breadth using different vaccine modalities. Assays, tools, and data generated will nucleate an open-access library and serve as a starting point for emergent CoV vaccine development.

1. Introduction

Coronaviruses (CoVs) are a large and diverse group of enveloped, positive-sense, single-stranded RNA viruses that sporadically spillover to humans from other animal hosts. When CoVs evolve the capacity for sustained human-to-human transmission, spillover events can result in epidemics, pandemics, or endemicity. To date, nine coronaviruses are known to infect humans. Of these, OC43, NL63, 229E, and HKU1 are endemic and associated with common cold-like symptoms. Middle East respiratory syndrome coronavirus (MERS-CoV) continues to spillover from camels, causing severe disease in humans, with sustained transmission in hospital outbreaks [1,2]. SARS-CoV-1 caused an epidemic from 2002 to 2004 [3], and SARS-CoV-2 a pandemic between 2020 and 2023 [4]. In addition, CCoV-HuPn-2018 and PDCoV have caused sporadic human infections [5].

CoVs also infect a wide range of mammalian and bird species, many that live in close proximity to humans. Their ability to infect diverse hosts is facilitated by high genomic plasticity driven by frequent mutation and recombination events, which enables adaptation to new hosts and environments, as well as a reliance on relatively well-conserved cell receptors among hosts [6]. The risk of spillover to humans or other new hosts is amplified in environments where animal interactions occur at high frequency, such as in live animal markets, wildlife and fur farms, factory farms, and areas with deforestation or other high-impact land use changes [6].

The spillover of CoVs into humans will continue and perhaps

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intensify [7], highlighting the need for rapidly available countermeasures in such events. The Coalition for Epidemic Preparedness Innovations (CEPI) aims to accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic threats, so they are accessible to all people in need. Core to its strategy is the 100 Days Mission: a goal spearheaded by CEPI and embraced by the G7, G20, and industry leaders, to accelerate the time taken to develop safe, effective, globally accessible vaccines against new threats to just 100 days. To meet this goal, preparedness activities must be initiated ahead of outbreaks. One such activity is the development of 'Vaccine Libraries', aiming to generate and share scientific tools and knowledge, including antigen designs and vaccine characterization data for multiple viral families known to infect humans. Such a viral family-based approach has also recently been advocated for in WHO's framework for epidemic and pandemic research preparedness [8]. In this context, CEPI has created a Coronavirus Vaccine Library project to develop antigens and

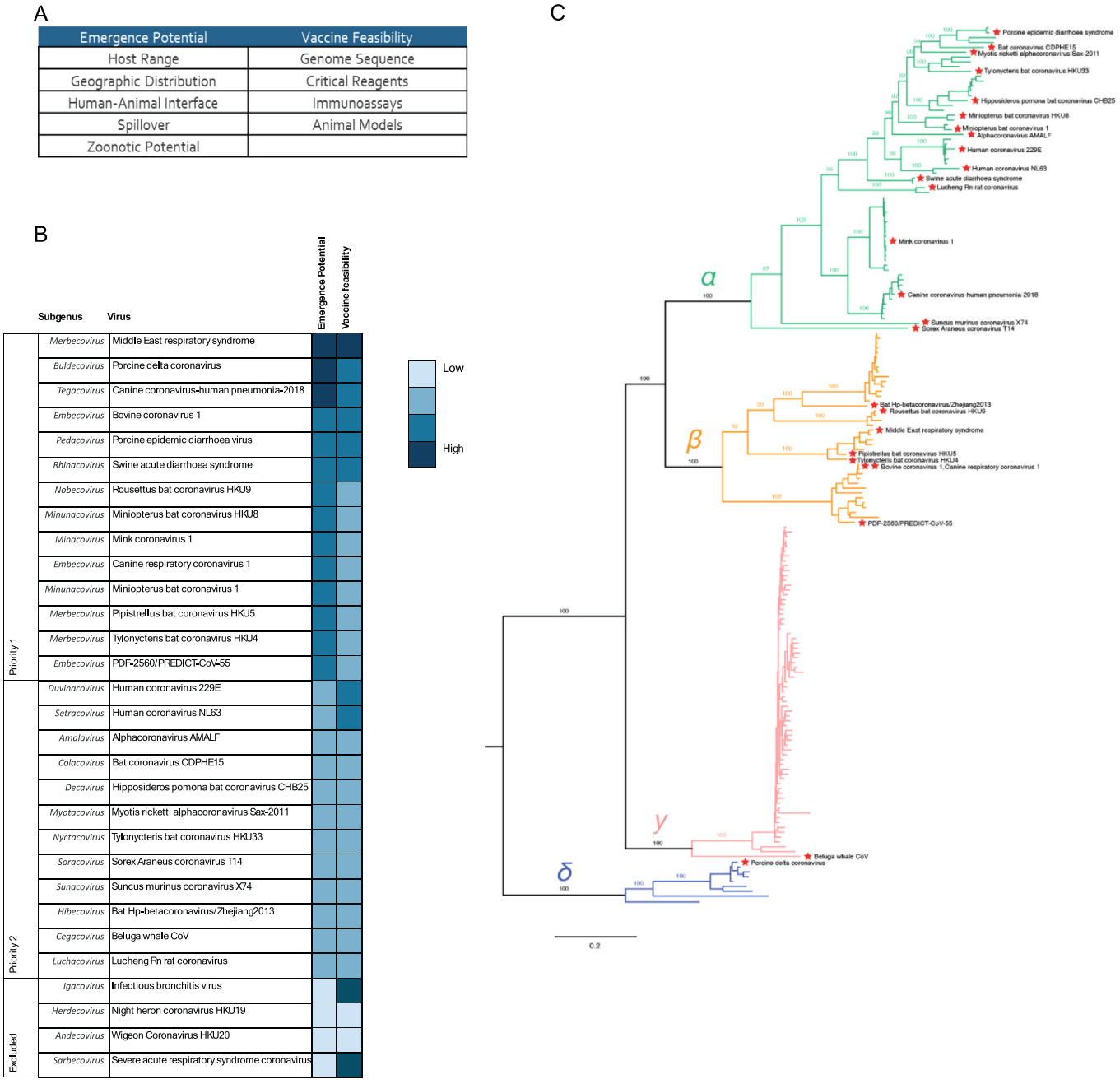

Fig. 1. Coronaviruses selected for inclusion in the Vaccine Library. A) Criteria used when prioritizing coronaviruses for selection, B) 'Risk scores' of coronaviruses assessed during prioritization exercise (assessed qualitatively), C) CoV phylogenetic analysis: all coronavirus sequences classified to the subgenus level were collected from NCBI/GenBank and the nsp12 through nsp14 region was extracted from each sequence. To capture the diversity of each subgenus in an unbiased way, sequences from each subgenus were then clustered at 95 % at the nucleotide level using cd-hit. One exemplar sequence from each cluster was translated and amino acid sequences were aligned using clustalo. A phylogenetic tree was then estimated using the maximum likelihood method in IQ-TREE2, employing the WAG+F + R6 model of amino acid substitution and 1000 ultra-fast bootstraps. Bootstrap values were removed below the subgenus level at the tips of the tree for clarity. Each genus (α, β, γ, δ) is designated with a separate colour and labelled on the preceding branch, while each subgenus is annotated with vertical lines on the right. Viruses selected for inclusion in the vaccine library are annotated with red stars. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

vaccine candidates for viruses across all four currently recognized genera of CoVs (α, β, γ, δ).

2. Selection of coronaviruses for prototype vaccine development

Despite extensive research into spillovers and the development of predictive tools [9,10], where, when, and what viruses will emerge as the next threat is unknown. Through the CoV Vaccine Library initiative, we aim to generate knowledge and tools to accelerate vaccine development against a wide range of CoVs, while prioritizing viruses with the highest assessed risk of spillover. The library should have enough prototype vaccine candidates — developed based on a representative 'prototype' pathogen — to allow for cross reactivity and/or rapid adaptation against any emergent coronavirus threat.

The large phylogenetic diversity of the *Coronaviridae* family (currently comprising 25 subgenera across α, β, γ, δ CoVs, although additional subgenera have been proposed [11]) presents a challenge for the selection and prioritization of prototype viruses for antigen discovery and vaccine development. To address this, a series of consultations with experts were hosted by CEPI to inform a selection of CoV prototype vaccine targets. Accordingly, a list of CoVs of interest was assembled using two main criteria (Fig. 1**A** and **B**). The first criterion, "emergence potential", was assessed qualitatively through expert discussions around available information on viral host range, geographic distribution, spillover opportunity at the human/animal interface, and documented spillover events. The second, "feasibility of research," considered practical considerations around the availability of the most basic information (*e.g.* genomic sequence) and tools to initiate prototype vaccine development. Based on these evaluations, 14 priority viruses were selected based on highest emergence potential and vaccine feasibility (Priority 1), with an additional 12 for consideration for subsequent prototype vaccine development (Priority 2) (**Supplementary Table 1**). Based on our analysis, the *Igacovirus*, *Herdecovirus*, and *Andecovirus* subgenera were excluded from representation given the low perceived emergence potential. In addition, due to the significant amount of knowledge and ongoing vaccine development addressing Sarbecoviruses (*i.e.*, SARS-CoV and SARS-CoV-2), we chose to exclude these as well. Finally, phylogenetic and antigenic diversity were considered to ensure that the coronavirus candidates selected were representative of the genetic diversity of the relevant subgenera **(**Fig. 1C**).**

3. Discussion

Through a series of consultations hosted by CEPI, a panel of CoV experts compiled a list of viruses for inclusion in a CoV Vaccine Library. The list of 26 selected viruses is intended to allow the scientific community to gather tools and knowledge to serve as a basis to accelerate the development of vaccines against future coronaviral threats. As more CoVs are identified and characterised, and new spillover events are documented, the vaccine library will need to be adapted to our evolving understanding of the family's diversity. While to our knowledge the vaccine library effort is the first of its kind, the CoV Vaccine Library complements the WHO's prioritized viral families by providing targeted coverage of coronaviruses, enhancing the global capacity to respond to future CoV threat [8].

The varied availability of epidemiological, genetic, and immunobiological data proved to be an obstacle for translating placement on the CoV phylogeny into a relevant and prototype vaccine candidate. Although some of the viruses selected have spilled over to cause disease in humans, information on human pathogenesis was limited, and could only be inferred from existing human CoVs or disease presentation in their animal hosts. Little is known about our baseline immunity against the vast coronaviral family, how our vulnerabilities have been altered post-COVID-19 pandemic and how they may vary geographically. Such information could help further prioritize vaccine library targets. Furthermore, the expected breadth coverage of each prototype vaccine developed will need to be characterised in order to ensure adequate coverage of the phylogeny. Finally, while some viruses such as SARS-CoV-2 and MERS-CoV are well-characterised, others have a limited number of or only partial sequences available in public databases potentially complicating vaccine design. Geographically, the panel of experts highlighted a gap in surveillance and sequencing data in South America and Africa. This and limited knowledge of antigenic diversity within the subgenera may lead to future selection of additional viruses for appropriate coverage.

PEDV, PDCoV, bovine CoV, and CCoV have caused significant outbreaks in farmed and companion animals, respectively. The veterinary vaccine field has developed several licensed vaccines or preclinical candidates for CoVs that pose a threat to livestock, notably, academic institutions in China have advanced numerous candidates to preclinical proof of concept [12]. Existing veterinary vaccines may not easily translate for human use due to differences in preferred vaccine platforms, regulatory standards, registration/licensing processes and differing cost of goods assumptions. However, an opportunity exists for the fields of veterinary and human vaccinology to learn from each other, collaborate on assays, reagents, and model development, and in some cases, dual-use vaccines could be considered [13].

Where preclinical data are limited or unavailable, the *in silico* design of spike proteins can serve as a starting point for the development of prototype vaccines. Pre-fusion stabilization of spike proteins through the introduction of prolines, disulfides or other mutations has been shown to enhance immunogenicity of coronaviruses spike proteins, as exemplified by efforts in SARS-CoV-2 and MERS-CoV [14,15] vaccine development. Computational prediction of stabilizing mutations could allow for rapid vaccine adaptation and design. Furthermore, although the initial library will focus on spike-based vaccines, conserved antigens with the potential to induce broadly reactive T cell responses should eventually form part of a comprehensive library strategy as well.

Early-stage development of these prototype vaccines will require investments in tools, assay, and model development, as well as careful thinking around balancing the need for gathering critical data and biosafety considerations. Vaccine design, production and pre-clinical immunogenicity testing can be performed without incurring significant biosafety risks. However, some gold standard *in vitro* assays, as well as pre-clinical vaccine efficacy testing, require the handling of live virus. A thoughtful risk-benefit assessment must be made when deciding to carry out such activities. Centralization of capabilities to laboratories with well-established and internationally agreed upon biosafety standards will be critical.

CEPI is assembling an online database (Disease X Knowledge Base) to house vaccine libraries, including the CoV library. The CoV vaccine library's goal is to aggregate all data relevant to vaccine development, centralizing the information and facilitating access. Artificial intelligence (AI) and large-language models are being developed utilizing an agentic agent framework with the goal to create an AI-based co-scientist using a federated learning framework that will allow users to query the database and rapidly access information, generate hypotheses and vaccine designs for emergent viruses that will build upon the growing knowledge base.

Given the inevitability of continued zoonotic spillovers from coronaviruses, proactive preparedness is essential to mitigate future pandemic threats. The accelerated development of COVID-19 vaccines, informed by prior work on MERS-CoV immunogens, underscores the value of prototype-based vaccine strategies [16]. Although efforts to establish vaccine libraries represent a step toward accelerating the adaptation and development of vaccines in response to emerging threats, the complexity of achieving equitable and accelerated outbreak vaccine deployment cannot be overstated, with its success depending on multidisciplinary, multi-institutional, and in many cases, international collaboration and cooperation at the global level.

CRediT authorship contribution statement

Dory Kovacs: Writing – review & editing, Writing – original draft, Investigation. **Gurpreet Brar:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Simon J. Anthony:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Lin-Fa Wang:** Writing – review & editing, Methodology, Investigation. **Edward C. Holmes:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Linda J. Saif:** Writing – review & editing, Methodology, Investigation. **Volker Gerdts:** Writing – review & editing, Investigation. **Leo Poon:** Writing – review & editing, Methodology, Investigation. **Stanley Perlman:** Writing – review & editing, Investigation. **Joris Vandeputte:** Writing – review & editing, Investigation. **Christian Drosten:** Writing – review & editing, Investigation, Data curation. **Heather Louise Wells:** Writing – review & editing, Visualization, Investigation. **Javier Castillo-Olivares:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Trevor Brasel:** Writing – review & editing, Methodology, Investigation. **Timothy Endy:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Ann-Muriel Steff:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Georges Thiry:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Nadia Cohen:** Writing – review & editing, Writing – original draft, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dory Kovacs and other CEPI employees report financial support (salaries) provided by Coalition for Epidemic Preparedness Innovations UK Limited. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.128140.

Data availability

Data will be made available on request.

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