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Predicting the next pandemic: VACCELERATE ranking of the *World Health Organization's Blueprint for Action to Prevent Epidemics*

Jon Salmanton-García [a,b,c,*], Pauline Wipfler [a,b,c], Janina Leckler [a,b,c], Pontus Nauclér [d,e], Patrick W. Mallon [f,g,h], Patricia C.J.L. Bruijning-Verhagen [i], Heinz-Joseph Schmitt [a,b,c,j], Ullrich Bethe [a,b,c], Ole F. Olesen [k], Fiona A. Stewart [a,b,c], Kerstin Albus [a,b,c], Oliver A. Cornely [a,b,c,l], on behalf ofon behalf of the VACCELERATE Consortium

[a] *Institute of Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University Hospital Cologne, Faculty of Medicine, University of Cologne, Cologne, Germany*
[b] *Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), University Hospital Cologne, Faculty of Medicine), University of Cologne, Cologne, Germany*
[c] *German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany*
[d] *Division of Infectious Diseases, Department of Medicine, Karolinska Institutet, Solna, Stockholm, Sweden*
[e] *Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden*
[f] *School of Medicine, University College Dublin, Dublin, Ireland*
[g] *Department of Infectious Diseases, St. Vincent's University Hospital, Dublin, Ireland*
[h] *Centre for Experimental Pathogen Host Research (CEPHR), University College Dublin, Dublin, Ireland*
[i] *Department of Epidemiology, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, Netherlands*
[j] *Global Health Press Pte. Ltd., Singapore*
[k] *European Vaccine Initiative (EVI), Heidelberg, Germany*
[l] *University of Cologne, Faculty of Medicine and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), Cologne, Germany*

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ABSTRACT

Introduction: The *World Health Organization (WHO)'s Research and Development (R&D) Blueprint for Action to Prevent Epidemics*, a plan of action, highlighted several infectious diseases as crucial targets for prevention. These infections were selected based on a thorough assessment of factors such as transmissibility, infectivity, severity, and evolutionary potential. In line with this blueprint, the VACCELERATE Site Network approached infectious disease experts to rank the diseases listed in the *WHO R&D Blueprint* according to their perceived risk of triggering a pandemic. VACCELERATE is an EU-funded collaborative European network of clinical trial sites, established to respond to emerging pandemics and enhance vaccine development capabilities.
Methods: Between February and June 2023, a survey was conducted using an online form to collect data from members of the VACCELERATE Site Network and infectious disease experts worldwide. Participants were asked to rank various pathogens based on their perceived risk of causing a pandemic, including those listed in the *WHO R&D Blueprint* and additional pathogens.
Results: A total of 187 responses were obtained from infectious disease experts representing 57 countries, with Germany, Spain, and Italy providing the highest number of replies. Influenza viruses received the highest rankings among the pathogens, with 79 % of participants including them in their top rankings. Disease X, SARS-CoV-2, SARS-CoV, and Ebola virus were also ranked highly. Hantavirus, Lassa virus, Nipah virus, and henipavirus were among the bottom-ranked pathogens in terms of pandemic potential.
Conclusion: Influenza, SARS-CoV, SARS-CoV-2, and Ebola virus were found to be the most concerning pathogens with pandemic potential, characterised by transmissibility through respiratory droplets and a reported history of epidemic or pandemic outbreaks.

* Corresponding author. University of Cologne, Faculty of Medicine and University Hospital Cologne, Institute of Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany.
E-mail address: jon.salmanton-garcia@uk-koeln.de (J. Salmanton-García).

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1. Introduction

In 2016, the *World Health Organization (WHO)* released the initial *Research and Development (R&D) Blueprint for Action to Prevent Epidemics*, which was created in consultation with experts in the field [1]. The *WHO R&D Blueprint* [2] identified several infections as high priorities for prevention, including Crimean-Congo haemorrhagic fever, Ebola virus disease, Marburg virus disease, Lassa fever, Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), Nipah and henipaviral diseases, Rift Valley fever, Zika virus disease, and Disease X [3]. After the declaration of the coronavirus disease 2019 (COVID-19) pandemic in March 2020 [4], the list was updated to include COVID-19 [2]. The selection of diseases for the blueprint took factors into account such as human-to-human transmissibility, severity or case fatality rate, the level of interaction between humans and animals, the public health context of affected areas, potential societal impacts, and the evolutionary potential of the pathogens [5]. Additionally, other organizations concerned with pandemic preparedness have also created their own compilations, such as Africa Centres for Disease Control and Prevention (Africa CDC) [6] or Coalition for Epidemic Preparedness Innovations (CEPI) [7] (Table 1). Of note, the *WHO R&D Blueprint for Action to Prevent Epidemics* did not prioritize the pathogens based on their likelihood of causing the next pandemic.

In response to the COVID-19 pandemic, the VACCELERATE vaccine clinical trial network was established in Europe in 2021 (www.vaccelerate.eu) [8–10]. This consortium has created a network capable of responding not only to COVID-19 but to other emerging pandemics and strengthening vaccine development capabilities across Europe. VACCELERATE's capacity mapping initiative resulted in the establishment of a Site Network comprising approximately 500 clinical trial sites in Europe, each equipped expertise in infectious diseases [9]. Preparing for the next pandemic requires that pathogens of pandemic potential are ranked and the next strategic steps of the VACCELERATE network prioritised.

The purpose of this survey was to classify the diseases listed in the *WHO R&D Blueprint for Action to Prevent Epidemics* based on the perceived risk of pandemic potential, with input from infectious disease experts from the VACCELERATE Site Network. The VACCELERATE consortium could then prepare for the design and develop of phase 2/3 clinical trials on the most relevant vaccination strategies.

Table 1
Pathogens identified as potential pandemic generators by Africa CDC, CEPI, WHO, and the current analysis.

Pathogens	Africa CDC [6]	CEPI [7]	WHO [1]	Current analysis
Anthrax	X			
CCHF virus	X		x	x
Chikungunya virus	X	x		
Dengue fever virus	X			
Disease X	X	x	x	x
Ebola virus	X	x	x	x
Hantavirus				x
Henipavirus				x
Influenza viruses				x
Lassa virus	X	x	x	x
Lyssaviruses	X			
Marburg virus	X		x	x
MERS-CoV		x	x	x
Monkeypox virus	X			
Morbillivirus	X			
Neisseria-meningitis	X			
Nipah virus		x	x	x
Poliovirus	X			
Rift Valley fever virus	X	x	x	x
SARS-CoV			x	x
SARS-CoV-2	X		x	x
Vibrio cholerae	X			
Yellow fever virus	X			
Yersinia pestis	X			
Zika virus			x	x

Africa CDC, Africa Centres for Disease Control and Prevention; **CCHF**, Crimean-Congo haemorrhagic fever virus; **CEPI**, Coalition for Epidemic Preparedness Innovations; **MERS-CoV**, Middle East respiratory syndrome coronavirus; **SARS-CoV**, severe acute respiratory syndrome coronavirus type 1; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus type 2; **WHO**, World Health Organization.

2. Methods

From February to June 2023, data were collected using an online electronic case report form, accessible at https://www.clinicalsurveys.net/uc/Next_pandemic/(EFS Fall 2022, TIVIAN, Cologne, Germany). All members of the VACCELERATE Site Network (https://vaccelerate.eu/site-network/) [9] were contacted via email and invited to share their infectious disease expertopinion. Other relevant infectious disease experts from outside of Europe were also contacted to obtain feedback at a global scale. Furthermore, the survey link was actively promoted through VACCERELATE's social media channels, including platforms such as LinkedIn® (https://www.linkedin.com/company/vaccelerate-eu) [11] and Twitter® (https://twitter.com/vaccelerate_eu) [12]

Each participant could rank the pathogens responsible for the diseases listed in the *WHO R&D Blueprint for Action to Prevent Epidemics* [2], including Crimean-Congo haemorrhagic fever virus, Disease X, Ebola virus, Lassa virus, Marburg virus, MERS causing coronavirus (MERS-CoV), Nipah virus, Rift Valley fever virus, SARS causing coronavirus type 1 (SARS-CoV), SARS causing coronavirus type 2 (SARS-CoV-2), and Zika virus. Infectious disease experts had also the option to include in their rankings three additional pathogens, namely hantavirus, henipavirus, and influenza viruses, and had the opportunity to add pathogens of their own consideration in the rankings. Each ranking could contain as many pathogens as considered, from a minimum of one up to 15 pathogens.

In the analysis phase, depending on the infectious disease expert ranking, points from 15 to 1 were assigned to the rank in reverse order. The pathogen with the highest perceived likelihood of triggering a pandemic was valued (1st position) with 15 points, while the pathogen considered with lowest likelihood to trigger a pandemic (15th position) received a single point (Table 2).

The resulting data were analysed and presented using frequencies, percentages, and appropriate ranges to provide a clear overview of the findings.

3. Results

A total of 187 responses were obtained from individuals representing 57 different countries. Among the countries providing the highest number of responses, Germany accounted for 27 replies (14.4 %), followed by Spain with 20 replies (10.7 %), and Italy with 14 replies (7.5 %).

In terms of the pathogens with the highest perceived likelihood of triggering a pandemic, influenza viruses received the highest positions in the classifications. Out of the 187 participants, 147 infectious disease experts (78.6 %) included influenza viruses in their top rankings, ranging from 1st to 4th positions. Disease X was selected 92 times (49.2 %) ranging from 1st to 9th place, while SARS-CoV-2 was included in 81 rankings (43.3 %) spanning from 1st to 14th place. SARS-CoV was ranked 41 times (21.9 %), occupying positions from 1st to 13th, and

Table 2
Ranking and voting system description.

List of pathogens to be ranked	*Available for experts*		*Available for analysts*
	Ranking		**Assigned points**
CCHF virus1.	1st	=	15
Disease X	2nd	=	14
Ebola virus	3rd	=	13
Hantavirus	4th	=	12
Henipavirus	5th	=	11
Influenza viruses	6th	=	10
Lassa virus	7th	=	9
Marburg virus	8th	=	8
MERS-CoV	9th	=	7
Nipah virus	10th	=	6
Rift Valley fever virus	11th	=	5
SARS-CoV	12th	=	4
SARS-CoV-2	13th	=	3
Zika virus	14th	=	2
Other pathogen*	15th	=	1

The experts who took part were able to rank a total of 15 pathogens, including up to 14 pre-selected pathogens and one additional pathogen suggested by them. They were required to rank at least one pathogen and could include a maximum of 15 pathogens in their rankings. During the analysis phase, different points were assigned based on the rankings given by the experts. These points were utilized to determine the overall ranking, as shown in Table 3.
CCHF, Crimean-Congo haemorrhagic fever virus; **MERS-CoV**, Middle East respiratory syndrome coronavirus; **SARS-CoV**, severe acute respiratory syndrome coronavirus type 1; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus type 2.
* Determined or suggested by the respective expert.

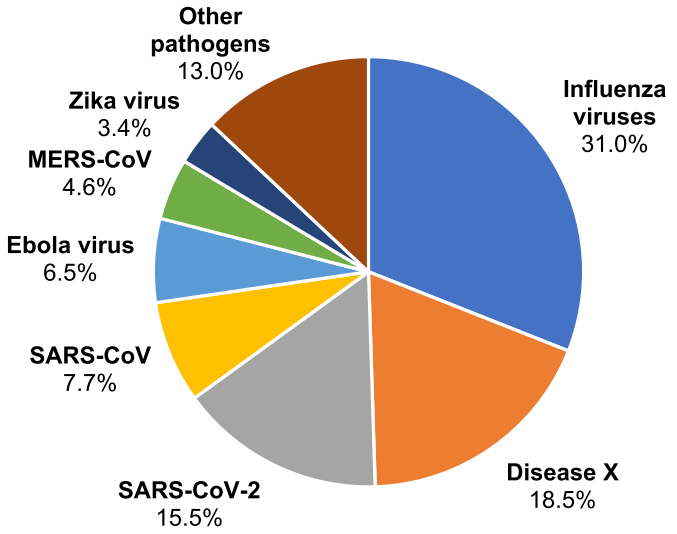

Fig. 1. Percentage of the overall points obtained by the respective pathogen. Other viruses include Crimean-Congo haemorrhagic fever virus, Marburg virus, Hantavirus, Lassa virus, Nipah virus, henipavirus, and Rift Valley fever virus. **MERS-CoV**, Middle East respiratory syndrome coronavirus; **SARS-CoV**, severe acute respiratory syndrome coronavirus type 1; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus type 2.

Ebola virus 36 times (19.3 %) ranging from 1st to 9th place. These findings position them as the top five pathogens overall based on the survey responses. The rankings of the top five pathogens did not show significant variations across different countries nor continents (Table 3, Fig. 1).

Among all responses, three pathogens consistently did not reach the top ranking. The Marburg virus achieved an overall ranking of 9th (with the highest rank being 2nd and the lowest rank being 13th), henipavirus ranked 12th overall (with the highest rank being 5th and the lowest rank being 14th), and Rift Valley fever virus ranked 13th overall (with the highest rank being 3rd and the lowest rank being 14th). The bottom 5 rankings in terms of perceived likelihood of triggering a pandemic included hantavirus and Lassa virus, both ranked 10^{ths}. Nipah virus received a rank of 12th, while henipavirus ranked 13th, and Rift Valley fever virus ranked 14th (Table 3). Single participants also raised concern on pathogenic fungi.

4. Discussion

In a survey with 187 responses from 57 countries aiming to rank the diseases listed in the *WHO R&D Blueprint for Action to Prevent Epidemics* based on the perceived risk of pandemic potential, influenza viruses received the highest rankings among the pathogens, with 79 % of participants including them in their top rankings. Disease X, SARS-CoV-2, SARS-CoV, and Ebola virus also ranked prominently. The rankings of the top five pathogens did not vary significantly across countries. Three pathogens, namely Marburg virus, henipavirus, and Rift Valley fever virus, consistently ranked lower and did not reach the top positions.

In comparison to the *WHO R&D Blueprint* [2], we included three additional pathogens to be ranked: influenza viruses, hantavirus, and henipavirus. Among these, influenza viruses not only outperformed the

Table 3
Overall ranking of analysed pathogens.

	Overall ranking	Points	% of points	Times voted	Maximum points	Minimum points	Highest ranked position	Lowest ranked position	Voted by x % of the participants
Influenza	1	2154	31.0 %	147	15	12	1	4	79 %
Disease X	2	1282	18.5 %	92	15	7	1	9	49 %
SARS-CoV-2	3	1076	15.5 %	81	15	2	1	14	43 %
SARS-CoV	4	532	7.7 %	41	15	3	1	13	22 %
Ebola virus	5	439	6.3 %	36	15	7	1	9	19 %
MERS-CoV	6	319	4.6 %	27	15	5	1	11	14 %
Zika virus	7	235	3.4 %	22	15	2	1	14	12 %
CCHF virus	8	201	2.9 %	18	15	6	1	10	10 %
Marburg virus	9	170	2.4 %	17	14	3	2	13	9 %
Hantavirus	10	144	2.1 %	15	15	4	1	12	8 %
Lassa virus	10	144	2.1 %	14	15	4	1	12	7 %
Nipah virus	12	122	1.8 %	13	15	3	1	13	7 %
Henipavirus	13	65	0.9 %	9	11	2	5	14	5 %
Rift Valley fever virus	14	57	0.8 %	8	13	2	3	14	4 %

Pathogens considered relevant by individual participants are omitted from this table due to their low frequencies.
CCHF, Crimean-Congo haemorrhagic fever virus; **MERS-CoV**, Middle East respiratory syndrome coronavirus; **SARS-CoV**, severe acute respiratory syndrome coronavirus type 1; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus type 2.

pathogens in the *WHO R&D Blueprint* [2] but also secured the top spot, surpassing the next pathogen on the list, which was Disease X. Hantavirus ranked 10th, and henipavirus ranked 13th, placing it just above Rift Valley fever. Although these three pathogens are currently not included in the *WHO R&D Blueprint*, they are indeed recognised as diseases of concern [1]. These findings might lead to a potential inclusion of these three pathogens in the *WHO R&D Blueprint* [2], particularly influenza viruses. The consideration of the previous epidemics caused by influenza viruses, with several pandemics and outbreaks occurring over the last 50 years period, might be an argument in favour of the inclusion of influenza [13–15]. Nevertheless, the absence of influenza from the *WHO R&D Blueprint* [2] may be attributed to the existence of numerous influenza vaccines and the distinct research and development (R&D) requirements associated with this disease when compared to other pathogens.

Disease X represents the awareness that a severe international epidemic could be caused by a pathogen that is currently unknown to cause human disease, without being associated with a specific pathogen [16]. Thus, it is challenging to prevent something of unknown nature, but it also provides a broad scope for rankings such as ours. To enhance pandemic preparedness for a potential Disease X outbreak, the VACCELERATE consortium has implemented a ready-to-use Site Network [9] and Volunteer Registry [8]. These innovative measures have significantly reduced the time required to enrol clinical trial sites and trial volunteers by up to six months [8–10]. Additionally, the consortium is actively working on developing specific protocols that can be swiftly activated and modified as needed during a disease outbreak. This comprehensive approach encompasses not only respiratory illnesses but also addresses diverse disease types such as diarrheal diseases [17], invasive fungal infections (including *Candida auris*) [18], neurotropic pathogens [19,20], and orthopox infections [21]. Furthermore, the VACCELERATE consortium recognizes the influence of climate change on disease patterns, including the potential spread of vectors into previously unaffected regions.

Both SARS-CoV and SARS-CoV-2 have already demonstrated their potential for causing pandemics, with outbreaks occurring in 2002–2004 [22] and an ongoing pandemic from 2019 [23], respectively. The fact that the data for this survey were collected during the final months of the COVID-19 pandemic might have influenced their high ranking. The global burden on healthcare systems has been substantial [24,25], and it is expected that SARS-CoV-2 may continue to be a seasonal virus of interest [26], similar to influenza viruses. The relatively rapid mutation rate of the virus [27] may also have contributed to its high ranking.

Since the discovery of the Ebola virus in 1976, almost 30 outbreaks have been documented [28], primarily confined to single countries, with the Democratic Republic of Congo experiencing most of the outbreaks, and the Republic of Congo, Gabon, Sudan and Uganda having experienced other relevant outbreaks. Guinea, Liberia, and Sierra Leone have been described as the origin of the outbreak from 2013 to 2016, with global concern and expansion [29,30]. It is crucial to mention that Ebola virus transmission beyond Africa during the 2013–2016 outbreak was limited to hospital settings and restricted to patient care dynamics [31]. The relatively recent occurrence of this global outbreak, which may have triggered increasing awareness about the pathogen, may have influenced its high ranking in our list [32]. It is worth noting that we received responses from only three African countries (Madagascar, Mauritius, and South Africa), origin continent of the Ebola virus [28], none of which have historically reported local outbreaks. One can propose that an increased representation of African participants might have contributed to a more prominent recognition of the impact of the Ebola virus infection. Additionally, the virus's ranking can be linked to its highly transmissible nature. However, it's important to acknowledge that the ease of transmission might be influenced by the specific geographical context. As part of an ongoing endeavour, this study will be repeated at regular intervals. By examining the findings of the subsequent iterations, it will be possible to determine whether the Ebola virus continues to be regarded as a highly pandemic-prone virus and why.

The remaining pathogens have demonstrated their pandemic potential to a lesser extent, with a more reduced number of outbreaks or none at all [33–39]. Furthermore, their rankings below the above-mentioned pathogens might have been influenced by the fact that most of them require close contact with infected animals such as bats, rodents, and primates, which may not occur that commonly in the countries where most of participating infectious disease experts come from. The ranking of each pathogen may have been significantly influenced by the personal clinical and research experience and expertise of the participating researchers. In future analyses, it may be necessary to inquire about the reasoning behind the specific rankings.

The analysis carried out by the VACCELERATE consortium holds significant promise for influencing pandemic preparedness. By evaluating the pandemic potential of various pathogens based on infectious diseases expert perception, the analysis becomes a valuable instrument for prioritizing future clinical trials, specifically in phases 2 and 3. These trials might be focused in the development of effective preventive and therapeutic interventions against the identified pathogens. The analysis plays a critical role in guiding preparedness initiatives and optimizing resource allocation to mitigate the impact of potential outbreaks. VACCELERATE already demonstrated its ability to respond swiftly to emerging threats, as evidenced by its diagnostic and treatment capacity mapping during the onset of the 2022–2023 mpox outbreak [40]. This initiative not only identified the observed risks but also highlighted the populations at risk during the initial stages of the outbreak [41]. This rapid response showcases VACCELERATE's proactive approach and effectiveness in assessing and addressing emerging infectious disease threats.

Nevertheless, this study has certain limitations that should be acknowledged. Firstly, only a limited number of the VACCELERATE Site Network members participated, representing approximately one-fourth of the total. This could be attributed to the remaining high workload resulting from the COVID-19 pandemic at the time of the invitations. Moreover, our results suffer from a lack of participation from infectious disease experts in Africa and Asia, despite the fact that most outbreaks related to the analysed pathogens have occurred on these continents. Future ranking initiatives should prioritize incorporating perspectives from Africa and Asia, which could potentially influence the final ranking of different pathogens. In order to obtain extensive feedback from these continents, it may be necessary to establish close partnerships with local institutions and ensure the survey is translated into languages other than English. Furthermore, it is worth noting that a substantial number of participants from European countries, specifically Germany, Spain, and Italy, were included. This demographic composition could potentially impact the overall perspective on the viral infectious burden, as highlighted in the study. Additionally, the exclusion of certain viruses with seasonal epidemic potential, especially in certain populations at risk, such as parainfluenza viruses [42] and respiratory syncytial virus (RSV) [43] in the survey should be acknowledged. Future studies and ranking initiatives may need to warrant their consideration to provide a more complete assessment of their epidemic potential. Lastly, the online data collection method may have introduced bias by excluding infectious disease experts with limited internet access.

In conclusion, infectious disease experts consulted from the VACCELERATE Site Network have identified influenza, SARS-CoV, SARS-CoV-2 and Ebola virus as the pathogens with the most worrisome and greatest potential to give rise to new pandemics. These pathogens possess easy transmissibility, primarily through respiratory droplets in the air, and have already demonstrated epidemic or pandemic capabilities.

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Data availability

Data can be made available upon request following the paths described in the manuscript.

Ethics approval

Not applicable.

CRediT authorship contribution statement

Jon Salmanton-García: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Pauline Wipfler:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Janina Leckler:** Methodology, Writing – review & editing. **Pontus Nauclér:** Methodology, Writing – review & editing. **Patrick W. Mallon:** Methodology, Writing – review & editing. **Patricia C.J.L. Bruijning-Verhagen:** Methodology, Writing – review & editing. **Heinz-Joseph Schmitt:** Methodology, Writing – review & editing. **Ullrich Bethe:** Methodology, Writing – review & editing. **Ole F. Olesen:** Methodology, Writing – review & editing. **Fiona A. Stewart:** Methodology, Writing – review & editing. **Kerstin Albus:** Methodology, Writing – review & editing. **Oliver A. Cornely:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Software, Supervision, Writing – review & editing.

Declaration of competing interest

Authors reports no conflicts of interest regarding the current manuscript.

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