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Unfinished business: Lessons for future G20 meetings on a more inclusive understanding of universal health coverage

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Abstract: The Group of 20 (G20) Osaka Summit in 2019 was a large step forward for global health diplomacy to build consensus on universal health coverage (UHC). To strengthen multi-stakeholder UHC partnership, Japan involved the research and policy advice network for G20 (Think 20: T20), civil society (Civil 20: C20), private initiatives of medical professional groups (H20), and the pharmaceutical sector. We attempted to identify UHC-related issues addressed and left unaddressed at the G20 Osaka, to bring lessons for future G20. We reviewed the G20 Osaka Leaders' Declaration, policy-related statements, and voices of the relevant G20 engagement groups and sectors. In July 2019, after the G20 Osaka Leaders' Summit, we organized an expert meeting convening Japan-based UHC-related key global health stakeholders. This review provides record of main findings presented in form of classifying the voices expressed in the meeting by UHC-related topics, and definitional ranges of UHC summarized. The T20, H20, and the pharmaceutical sector noted during our expert meeting that the ministerial-level health-finance collaboration was one of the key agendas suggested at the G20. T20 and C20 called for a recognition of health needs of refugees, migrants and other vulnerable groups in achieving UHC. Sexual and reproductive health and rights (SRHR) with a human rights-based approach through UHC was raised by the C20 as an issue unaddressed in G20 Osaka. Variation in operative purposes between global health stakeholders led to a definitional difference in the scope of UHC. The definitional difference could delay progress of UHC attainment. Addressing migrant and refugee health and SRHR within the context of UHC is further needed. Understanding perspectives of various stakeholders will become increasingly important to well-coordinate multi-actor cooperation with adequate social responsibility and transparency in UHC achievement and public-private partnership. In future G20, for UHC in the COVID-19 pandemic and post-pandemic worlds there is need of *i*) ensuring an integrated yet comprehensive multi-stakeholder approach towards UHC; *ii*) incorporating important dimensions such as the marginalized population and gender; and *iii*) ensuring adequate investments toward health information systems and governance to track health data for the vulnerable population and gender-responsive financing.

***Keywords*:** G20, universal health coverage, global health, health policy, United Nations high-level meeting, global health diplomacy

Introduction

The Group of 20 (G20) Osaka Summit in May 2019 was the last G20 meeting held before the coronavirus disease 2019 (COVID-19) pandemic and was a remarkable milestone for global health diplomacy to reach a consensus on promoting universal health coverage (UHC). Before then, UHC was only brought up slightly in other G20 meetings, along with the content on safeguarding against health crisis and strengthening health systems in 2017 (*1*), and no single paragraph existed for UHC in the Leaders' Declarations agreed by G20 countries in 2018 (*2*). During the 2019 G20 Summit, however, UHC was brought up clearly to recall its commitment for achievement according to national contexts and priorities, in the *G20 Osaka Leaders' Declaration* (*3*). Moreover, in recognizing the importance of sustainable financing for health, the *G20 Shared Understanding on the Importance of UHC Financing in Developing Countries* (*4*) was adopted

to reaffirm commitment for UHC among the Finance and Health Ministers at their Joint Session, which was simultaneously held during the G20 Osaka Summit (*5*).

Uniquely taking opportunity of the G20 presidency in 2019, Japan took a whole-of-society approach in order to strengthen partnerships and engage in policy dialogues with G20 Engagement Groups. The official G20 Engagement groups include research and policy advice network for the G20 (Think 20: T20) (*6,7*) and the civil society (Civil 20: C20) (*4*). The G20, T20, and C20 have each published their declaration in relations to G20 (*6-8*). In addition, private initiatives of medical professional groups from the Health Professional Meeting (H20) organized by the World Medical Association (WMA) and Japan Medical Association (JMA) presented their respective memorandum (*9*), and the pharmaceutical sector driven by the International Federation of Pharmaceutical Manufactures and Associations (IFPMA) including companies in Japan, the United States, and Europe published a statement (*10*) to Japan's Prime Minister Shinzo Abe in order to accelerate progress towards UHC among all United Nations (UN) member states. Following the G20, the first-ever UN High Level Meeting (UN-HLM) on UHC was held on September 23rd, 2019, where a political declaration on UHC was adopted by all UN member states. This marked a turning point in the history of global health diplomacy, placing UHC as a major issue not only in global health but for the entire global community.

Bloom and colleagues of the T20 called on next steps to be taken for UHC in advance to the G20 Osaka Summit, highlighting that the G20 have made an effort to facilitate crucial actions for UHC (*6*). However, after the G20 Osaka Summit, issues remain awaited to be addressed in subsequent G20 meetings, requiring strengthened visibility for political momentum towards UHC and further understanding of perspectives or various global health stakeholders. There is also a lack of evidence regarding these remained issues in relations to the voices and statements of the G20 Osaka Summit Engagement Groups. Therefore, we attempt to identify UHC-related issues that were either addressed or left unaddressed at the G20 Osaka Summit. We also reflected upon outcomes of the first ever UN-HLM on UHC in September 2019, which followed after G20 Osaka Summit. Since then, much of the world's focus has shifted to pandemic preparedness and response with the emergence of COVID-19, but UHC remains to be a crucial issue to ensure health equity and prevent further health crises. Lessons learnt in this study were initially to be applied for at the G20 Riyadh Leaders' Summit in November 2020, yet they still remain as important lessons to be reflected in future G20, as many of the issues have been undealt with to date. We provide our review to substantially leverage effective UHC in its next miles of political history of global health diplomacy, including the G20 Rome taking place in October 2021 (*11*).

Identifying UHC related achievements and issues unaddressed

We reviewed the G20 Osaka Leaders' Declaration (*3*), and policy-related statements and voices of the relevant G20 engagement groups and sectors (the T20, C20, H20, and the pharmaceutical sector). In addition, an expert meeting was held by authors from the Institute for Global Health Policy Research (iGHP), National Center for Global Health and Medicine (NCGM) under the purpose of discussing the addressed and unaddressed issues at the G20 Osaka. This meeting was held on July 30th 2019, which was after the G20 Osaka and before the 2019 UN-HLM on UHC. The main speakers were Japan-based UHC-related key global health stakeholders from the G20, T20, C20, H20, and the pharmaceutical sector. Information obtained through this expert meeting were also fed into this paper by summarizing the voices from the discussion and answers to common questions (on what were "suggested and agreed by the 2019 G20", "issues not discussed enough at the 2019 G20", "issues to be discussed at the 2019 UN-HLM", and "issues to be discussed at the 2019 G20 Health Ministers Meeting").

We then classified the voices of the T20, C20, H20, and the pharmaceutical sector by UHC-related topics: health systems financing, service quality and delivery; inclusiveness; innovation; operational cooperation and partnership; and prioritization and sustainability, monitoring and evaluation. In addition, based on the stances taken by each of the stakeholders, we plotted the definitional ranges of UHC and perspectives in relations to the 2019 G20 Health Ministers' Meeting and the 2019 UN-HLM.

Varying understandings of UHC

Alongside the strengthened ministerial-level collaboration between health and finance sectors in the occasion of the G20 Osaka Leaders' Summit, diversified voices were heard among stakeholders, around issues related to monitoring and evaluation of progress towards UHC, actor cooperation between global health and medical entities, and partnership building. To take a further step into the discussion, stakeholders voiced the health needs of refugees, migrants and other vulnerable groups in achieving UHC, and the importance for realizing sexual and reproductive health and rights (SRHR) through UHC. Variation in operative purposes among global health stakeholders has resulted in varying scopes of key understanding behind UHC.

Diversified voices on UHC with health-finance collaboration agreed to be G20 Osaka's key agenda

While the G20 Osaka Leaders' Declaration called for greater collaboration between health and finance authorities, where its commitment was affirmed by the

G20 Finance and Health Ministers during their first-ever joint session at the G20 (*12*), diversified voices on UHC were heard among stakeholders. The T20, H20, and the pharmaceutical sector noted during our expert meeting that this health-finance collaboration was one of the key agendas suggested to the G20 (Table 1). However, according to the T20, the G20 failed to discuss enough on monitoring tools for prioritizing primary health care (PHC)-based health systems and a common mechanism to monitor UHC. The H20 brought up remaining challenges in cooperation among key global health actors, medical doctors, and medical associations (Table 2). The pharmaceutical sector emphasized the need to establish of a new public-private partnership (PPP) dialogue platform. In relations to partnerships, T20 emphasized the importance of effective coordination for sustainable UHC. C20 called for a comprehensive and effective review mechanism including independent evaluation of UHC by the civil society. Furthermore, the H20 raised further need in health-finance ministerial-level collaboration to promote UHC in developing nations, and the pharmaceutical sector requested to ensure commitment for progress towards UHC not only among G20 countries but among all UN member states.

Inclusive UHC to address migrant health and sexual and reproductive health and rights

In response to the last G20, both C20 and T20 called for a recognition of refugees, migrants and other vulnerable groups in achieving UHC (*4,8*). Migration and migrants' wellbeing are critical issues of the twenty first century (*13*). The T20 further called for data and statistical management of migrant health to understand their needs better and to be able to provide evidence-based policy to address the health needs of migrants (*6*), but the G20 Osaka left this issue unaddressed. While the Finance and Health Ministers' meeting in G20 Osaka recognized the need for "high quality primary healthcare services, including immunization, as well as essential medicines, [made] accessible to everyone", the document did not specify whether this includes migrants, regardless of legal and documentation status. The last G20 meeting seemed to only address UHC as a narrower scope that concerned only its citizens. The G20 countries, instead, can approach UHC from a human security perspective. Having this perspective would be the first step to ensure primary healthcare at an affordable cost to all, including migrants independent of their migratory or legal status.

Realization of SRHR through UHC was another issue proposed by the C20 but left unaddressed at the G20 Osaka Summit. Post G20 Osaka, SRHR was brought up in the political declaration of the UN-HLM in 2019 (*14,15*), and its necessity was re-emphasized by the joint press statement developed by 59 government agencies in response to SRHR and COVID-19 (*16*). The statement raises the need for sexual health services with a priority on funding for SRHR and clearly indicates that it is crucial that leaders recognize the central role of UHC in health emergencies and the need for robust health systems to save lives (*16*). The governmental level statement highlights the need for essential health workers and resources to respond to maternal and child mortality, unmet needs for reproductive health commodities including contraception, sexually transmitted diseases, and unsafe abortion (*16,17*).

Variation in definition and scope of UHC among stakeholders

The purpose of the UN-HLM and the G20 Health Ministers' Meeting have dimensional differentials in terms of definitional range of UHC, as well as its perspective regarding aid allocation, here simplified by a binomial dimension on the y-axis: whether it is donor-driven or is based on the recipient countries' needs and perspectives (Figure 1). In addition to the country-specific definition of UHC with an absence of global standardization (*18*), variation in operative purposes between global health stakeholders led to a definitional difference in the scope of UHC. As plotted on the x-axis, the narrowest definition of UHC would be in line with the Sustainable Development Goal (SDGs) 3.8, referring to indicators of service coverage and financial risk protection, namely the gold standards in monitoring and evaluating UHC (*19,20*). On the other hand, some global health actors recognize UHC as a broader concept, i.e., inclusive approaches of health-related issues in the SDGs or sometimes beyond (*21*).

The UN-HLM aims to prioritize accountability over resource efficiency, a clear distinction in comparison to the G20 Health Ministers' Meeting that served as an opportunity to discuss more technical issues regarding health resource allocation. While the importance of health as an agenda remains a small part in comparison to other G20 agendas. The G20 holds an inclusive stance in pinning the UHC definition and does not restrict its meaning to the narrow definition in SDG 3.8. As G20 is composed of advanced economies, we see its perspective closer to donor driven on the y-axis. On the contrary, the C20 presented a less donor driven perspective, and emphasized a further need for UHC to meet the needs of the socially and politically marginalized population. H20 was relatively similar to C20 in terms of perspective but was more technically oriented to promote cooperation between ministries of finance and ministries of health in recipient countries. They had a particular focus on health system strengthening and capacity development of human resources. T20 had a narrower definitional range of UHC compared to other stakeholders, as they emphasized the need for multisector cooperation among government, and their voices were centered around operational cooperation, partnership, and innovation. Objectively, T20 had a more donor driven perspective

Table 1. Voices of the T20, C20, H20, and the pharmaceutical sector on achievement of the G20 and undiscussed issues

Thematic area	Suggested and agreed by the G20 2019					Issues not enough discussed at the G20 2019				
	Voices	T20	C20	H20	P[*1]	Voices	T20	C20	H20	P[*1]
Health systems financing, service quality and delivery	Emphasizing health system strengthening while focusing on the quality of services				X	Health financing to achieve UHC		X		
	Strong PHC systems that can harness increased ageing and NCD related issues (integrated nursing and medicine with a community-based, life-course approach)	X				Domestic financing for health that reach the 5% GDP target or 15% of national budget, and elimination or minimalization of out of pocket payment		X		
	Strengthening human resource capacity for health and policy makers			X		Due to emergence of large multinational IT platform companies *etc*., financial redistributions among nations are decreasing, by factors such as the globalization of profit structure, or base erosion and profit shifting (BEPS). The fact that the *G20 Shared Understanding mentions* "financial capacity" and "progressivity" can be evaluated positively to some extent, but doubts remain on its effectiveness.		X		
	Strengthening of health systems with a focus on quality both by public and private sectors			X						
Inclusiveness	Countries with heavy disease burdens as well as political economic crises should not be left out of achievement of UHC		X			PHC for all people, especially for the marginalized population	X			
	UHC should be grounded on human rights-based approach, prioritizing PHC, ensuring SRHR, responding to gender-based violence, and adopting a holistic approach to health including nutrition and WASH		X			Documentation of migrants including health workforce mobility. Health protection for migrants.	X			
	Ensure UHC that leaves no one behind, including the most vulnerable and marginalized populations such as migrants and refugees, sexual minorities, MSM, sex workers, *etc*.		X			UHC that leaves no one behind, including socially and politically marginalized and vulnerable populations		X		
						Human rights and human security as a basis for UHC		X		
Innovation	Promotion of innovation through public private partnership/ cost effective and appropriate digital health	X								
Operational cooperation and partnership	Cooperation between health and finance ministers	X		X	X	Role of physicians and their associations to advocate and ensure UHC			X	
	Call for an effective partnership, Effective coordination for sustainable UHC	X		X		Establishment of new platform for public and private (and academia) partnership				X
	Recommending multilaterals and stakeholders to coordinate effectively				X					
Prioritization and sustainability, monitoring and evaluation	Recognizing the need for sustainable health financing		X	X		Monitoring tools for PHC-based health system	X			
	Each country should achieve 5% GDP for spending on heath, donor countries should achieve 7% ODA target and prioritize health. Ensure sustainability of GF, GAVI and other multilaterals through sufficient replenishment		X			Support for UHC indicator calculation. Common UHC monitoring mechanisms	X			
	Commitment to ensure UHC in accordance with each country situation				X					

[*1] P: Pharmaceutical sector. Abbreviations: UHC: universal health coverage; PHC: primary health care; SRHR: sexual reproductive health rights; WASH: water, sanitation and hygiene; MSM: men who have sex with men; GDP: gross domestic product; ODA: official development assistance; GF: Global Fund; GAVI: Gavi, The Vaccine Alliance.

Table 2. Voices of the T20, C20, H20, and the pharmaceutical sector on remaining challenges for the UN High-level Meeting and G20 Health Ministers' Meeting, 2019

Thematic area	Issues to be discussed at the UN High-level Meeting 2019					Issues to be discussed at the G20 Health Ministers Meeting 2019				
	Voices	T20	C20	H20	P[*1]	Voices	T20	C20	H20	P[*1]
Health systems financing, service quality and delivery	Financing for UHC, particularly on securing domestic financing and achieving 5% GDP target		X			Health financing, (Each country should achieve 5% GDP for spending on heath, donor countries should achieve 7% ODA for health, and prioritize health in their ODA policy)		X		
	Recognizing the importance of equitable system for revenue collecting		X			Access to essential medicines in developing countries, lower price setting and securing of new incentives		X		
	Ensuring access to medicine, by ensuring low or no out of pocket payment		X			Development of a process which minimizes the negative impact for middle income countries transitioning from donor funding to domestic funding for health finance resources to ensure UHC		X		
	Capacity development of health human resources as well as of policymakers			X		Securing sustainable health financing to ensure UHC			X	
	Strengthening of health systems with a focus on quality			X		Talent development for human resources for health to ensure UHC			X	
	Recognition for the importance and implementation of sustainable health finance			X						
Inclusiveness	Basis for UHC (human rights and human security), as well as achieving UHC that leaves no one behind		X			PHC for all people, especially for the marginalized population	X			
						Documentation of migrants including health workforce mobility, health protection for migrants	X			
Operational cooperation and partnership	Effective coordination for sustainable UHC	X				Partnership between physicians and their associations and governments as well as with WHO to ensure UHC			X	
	Recognition of civil society involvement in achieving UHC		X			Establishment of new platform for public and private (and academia) partnership				X
	Further coordination between health and finance ministries to ensure UHC in developing countries			X						
	Commitment to achieve UHC by all UN member states, not just G20 countries				X					
	Further coordination between health and finance ministries				X					
	Establishment of the Global Action by G20				X					
Prioritization and sustainability, monitoring and evaluation	Holistic review mechanism of UHC that includes an independent evaluation by CSOs		X			Monitoring tools for PHC based health system	X			

[*1] P:Pharmaceutical sector. Abbreviations: UHC: universal health coverage; PHC: primary health care; GDP: gross domestic product; ODA: official development assistance; WHO: World Health Organization; CSO: chief sustainability officer.

than C20 and H20, as the T20 suggested a strong PHC system to harness issues such as ageing and non-communicable disease, and public-private partnership.

Based on policy-related documents and voices from multi-stakeholders (Tables 1 and 2), we identified a narrower definition of UHC among T20 and H20, compared to G20 and C20, having a focus on monitoring UHC rather than evaluation for accountability. The T20 and H20 had a higher motivation to seek for further efficient resource allocation, through improvement of UHC indicators and partnerships. Issues on health information systems, especially for migrant health and their social security, were brought up by T20 as an issue undiscussed at G20. The C20 took an inclusive approach both in terms of UHC definition and donor-recipient perspective with attention on expanding the quality and

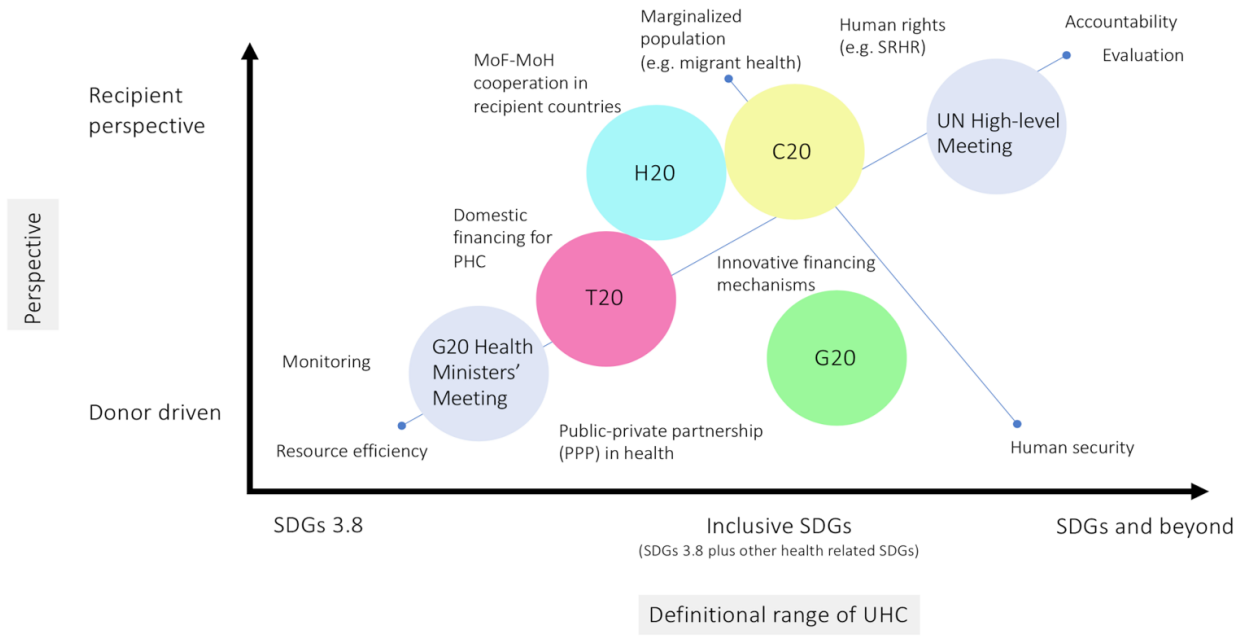

Figure 1. Definitional range of UHC and perspectives by key actors in relation to positions of high-level meetings. *Abbreviations*: UHC: universal health coverage; SDGs: Sustainable Development Goals; UN: United Nations; PHC: primary health care; SRHR: sexual and reproductive health rights; MoF: Ministry of Finance; MoH: Ministry of Health.

quantity of financing development assistance for health to reach the vulnerable and marginalized population such as migrants.

Challenges and solutions for a holistic understanding of UHC

Definitional differences in the scope of UHC among stakeholders were identified in our study. These differences pose challenge in attaining harmonization between aid agencies as well as alignment between donors and recipients and could further delay the achievement of UHC and the movement towards fulfillment of the SDGs. Addressing marginalized issues, such as migrant and refugee health and SRHR, within the context of UHC is needed. Nevertheless, they were unfortunately not brought up clearly as part of the official declarations in the event of the G20 Osaka Summit. In the future, understanding perspectives of the G20, T20, C20, H20, and the pharmaceutical sector will become increasingly important to well-coordinate multi-actor cooperation with adequate social responsibility and transparency in UHC achievement, to build a stronger PPP.

Migrant health and sexual and reproductive health and rights as a key issue for comprehensive commitment towards UHC

Amid the increase in multi-stakeholder platforms and partnerships, addressing vulnerable populations and issues such as migrant health and SRHR through an integrated definition that harmonize the vision and philosophy of UHC between stakeholders, may be a key issue for comprehensive commitment towards UHC. Given our results, all actors need to ensure the ownership of both donor and recipient countries among multi-stakeholders as well as a clearer UHC definition.

Despite the varying dependence and acceptance of migrants and refugees among the G20 countries, they recognized the growing migration trend as noted in the leader's declaration (*3*). With about one seventh of the world's population currently living in a country outside of where they were born (*22*), international effort is needed to explicitly address the health needs of migrants and refugees and to include them in the individual national health policies and plans in advancing "health for all" for UHC. In particular, healthy inequity that arise from economic, administrative, cultural and language barriers to healthcare that migrants face regardless of the legal or migratory status (*23,24*), should be addressed. The World Health Organization (WHO) also recognized that the SDG 3.8 on UHC cannot be achieved unless the health needs of migrants and refugees are met and health inequity is reduced (*25*). Yet, migrants' health still remain as a challenging issue as border control and health protection policies often have differing goals (*26*). Despite two World Health Assembly resolutions dedicated to the health of migrants in 2008 and 2017 (*27,28*), *the United Nations General Assembly High Level Meeting on Large Movements of Migrants and Refugees* in 2016, and the *Global Compacts on Refugees and Safe, Orderly and Regular Migration* adopted in 2018, many countries, including some of the G20 countries, do not

share a shared understanding on migrants' rights and do not recognize global frameworks for safe migration that protects migrants' welfare, including migrants' health. As for the *Global Compact for Safe, Orderly and Regular Migration*, which explicitly stated that health needs of migrants and refugees should be incorporated in national and local healthcare policies and plans, it was also not signed by several countries including the United States under the Trump administration (*29*), primarily due to economic and national security issues. Public health emergencies like COVID-19 may pose an opportunity for countries to re-examine the importance of extending access to healthcare to migrants and refugees to curve health inequity and combat health crises. For example, the United States and many other nations offered COVID-19 vaccines for free to all individuals residing in the country regardless of the immigration status (*30*). Such an understanding on the impact of the health protection of the vulnerable population should extend to the coverage of other essential health services to drive forward UHC.

The lack of international consensus on the definition of SRHR as well as family planning driven from its sensitiveness, makes its realization *via* a concept like UHC difficult. Reproductive health and rights were defined and agreed during the International Conference on Population and Development (ICPD) in 1994 among 179 states. However, ICPD neither defined sexual health nor explicitly referred to sexual rights while the conference assumed that reproductive health embraces sexual health. There have been several attempts to define sexual rights by some organizations, *e.g*. WHO (*31*) and the World Association for Sexual Health, but no definition has yet to reach an international consensus. The lack of international consensus regarding SRHR also lied in the family planning approach, principally in the right to safe abortion. Different beliefs have existed among the G20 member states where some members hold negative stances against for abortion. For example, the United States during the Trump administration decided to withdraw its support for federal funding for overseas family planning and reproductive health organizations that provide abortion services or counselling (*32*). The key for reaching an agreement on SRHR is to highlight several components of SRHR in association to a more widely recognized human rights that have definitional alignments of SRHR and family planning. It remains a challenge to standardize the definition in relation to diverse interpretation of safe abortion. However, given that there are also many components that the member states have already admitted, *e.g*. women and girls' rights and health care for women before and after pregnancy and childbirth, shedding more light on these areas would serve as the first step for member states to realize at least some of the components of SRHR through UHC.

Strengthening the national evidence-based monitoring and evaluation system

The UHC monitoring framework indicators, composed of service coverage (*19*) and financial risk protection (*20*) suggested by the WHO and the World Bank (WB) in 2013 (*33*), emphasizes the need to implement national evidence-based monitoring and evaluation systems that aim to attain country-comparability and national data representativeness (*34*). At the G20 Osaka Summit, this was reemphasized by countries of strong economy agreeing that investing in health at an early stage of development was important for sustainable and inclusive growth, thus encouraging developing countries to mobilize their domestic resources for UHC (*4*). At the same time, the digitalization of health data to track UHC indicators is needed, especially for developing nations that do not have a sufficient amount of quality data (*18,34*). Multi-stakeholder platforms and partnerships took a step to the next level where international coordination became more important, especially for aid recipient countries. International coordination is a crucial challenge in investment for global health due to the increasing role of the private financial sector actors (*35*). Financial outcomes of long-term funding among government institutions and multilateral agencies could lead to risk sharing among health infrastructure projects, for example, with better credit ratings and lower cost of capital (*36*).

Building further multi-stakeholder platforms and partnerships for UHC

In order to follow a global action plan for healthy lives and well-being for all, all relevant stakeholders need to collaboratively make effort for UHC through multi-stakeholder platforms and partnerships to support the efforts of member states, not only to achieve UHC but other health-related SDG targets. Multiple perspectives of the G20, T20, C20, H20, and the pharmaceutical sector need to be understood in order to well-coordinate its cooperation for higher participation and transparency in UHC achievement.

Furthermore, despite the countries' growing motivation towards UHC at the national level, there is an essential need for multi-stakeholder platforms and partnerships that ensure all donor and recipient countries to have ownership to further enhance UHC. The UHC 2030 serves as a knowledge hub to deliver experience-based or evidence-based resources bridging between the WHO and the WB. Through the UHC 2030, WHO and WB have the fundamental aim to further work together to share their strong networks with health ministers and finance ministers, as well as to exchange knowledge on health expertise and financial operations that are unique to their institutions.

In addition, finances need to be well coordinated, with synergy of traditional and innovative financing

mechanisms, including the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), Gavi, the Vaccine Alliance (GAVI), Global Financing Facility for Women, Children, and Adolescents (GFF), and the UN Trust for Human Security. Also, international platforms with innovative financing mechanisms *via* public-private partnerships, such as the Global Health Innovation and Technology Fund (GHIT), the Coalition for Epidemic Preparedness Innovation (CEPI), and the recently developed Access to COVID-19 Tool (ACT) Accelerator, should facilitate and propel the research and development of vaccines, pharmaceuticals and other essential medical commodities. In addition, these platforms should help with the knowledge sharing of resource mobilization to implementation through the lens of UHC in order to expand the service delivery of these essential commodities.

With limited public funding in health development assistance, the need for strengthening the partnerships among government institutions, the private sector, academia, and the civil society require enhanced emphasis on achieving UHC through traditional and innovative financing mechanisms. The coordination between the Secretary-General of the UN and the Member States to achieve synergistically UHC and all health-related targets of the SDGs would be a way forward in ensuring political momentum to achieve UHC by 2030, and to capture UHC-related targets outside SDG 3.8. including migrant health and SRHR.

Way Forward

At the time of writing, no G20 meetings have yet to thoroughly address the definitional differences identified in our study, including the G20 Riyadh Summit in 2020 and the Global Health Summit, which had taken place in Rome on 21 May 2021 as a pre-event of the G20 Health Ministers' Meeting 2021 and the G20 Rome Summit 2021. In midst of responding to the surging pandemic, the Leader's Declaration of G20 Riyadh Summit in 2020 noted that "well-functioning, value-based, inclusive, and resilient health systems are critical to move towards UHC achievement", and emphasized "the importance of UHC financing in developing countries" (*37*). The Rome Declaration, which was published as an output of the Global Health Summit in May 2021, underlined the need of "sustained investments in global health, towards achieving UHC with primary healthcare at its centre," amongst others, and listed principles as voluntary orientation for current and future action for global health including guiding commitments for UHC in its relations with the current pandemic and future potential public health emergencies (*38,39*). In conclusion, we raise the following three major points to be addressed through future G20 meetings, including the upcoming Rome Summit in October 2021.

First, there is need of ensuring an integrated yet comprehensive multi-stakeholder approach towards UHC, which could in some cases require efficient specialization between actors to overcome its definitional difference. Second, incorporating important dimensions such as the marginalized population and gender, in order for the progress of UHC to respond to structural inequity and leave no one behind, is important. Third, investments toward health information systems and governance to track health data for the vulnerable population and gender-responsive financing are effective, as demonstrated during the global spread of COVID-19.

Suggestions for future G20 Leaders' Summit beyond Riyadh from experiences of G20 Osaka

In order to take better action for UHC through future G20 summits, there is a need for ensuring an integrated yet comprehensive multi-stakeholder approach towards UHC. This could in some cases require efficient specialization between actors to overcome its definitional differences. Definitional alignment among various stakeholders is needed to reach international consensus on further promotion of UHC, as well as to address marginalized issues that have not been addressed at the G20 Osaka Summit. While between-country dialogue is crucial to effectively achieve UHC, dialogue on UHC between multi-stakeholders may also be a key in understanding how countries could together bring UHC to its next step.

Second, incorporating important dimensions such as the marginalized population and gender, in order to respond to structural inequity and leave no one behind, is important. In doing so, we need further commitment towards migrant and refugee health based on what has been agreed at the UN-HLM 2019, and towards SRHR stemming further upon the joint press statement on SRHR and COVID-19 agreed by government agencies of 59 countries calling for gender-responsiveness and multilateral efforts to respond well to COVID-19 (*16*).

Further ways of coordination for leadership towards digitalization of health data and optimal resource allocation

Third, investments toward health information systems and governance to track health data for the vulnerable population and gender-responsive financing are effective, especially with the global spread of COVID-19. Investments toward better health information systems and governance to track health data are solutions for better migrant and refugee health (*40*). Whilst COVID-19 is pushing forward investments in health for all amongst many countries (*41*), there is a need for well-coordinated health governance and policies with the social protection systems to protect the poorest and the vulnerable population groups that are facing further financial hardships due to the pandemic (*42*). For

example, with the COVID-19 pandemic, continuation of current lockdowns has increased gender-based violence and unintended pregnancies that require carefully thought-out preventive policies and actions to meet the SRHR needs (*43-45*).

Leadership towards digitalization of health records or infectious disease tracking mechanisms could be driven further by the technologically advanced countries and actors with a well-established PPP (*46*). For instance, rapid efforts to harmonize and digitalize personal health records for COVID-19 vaccine and negative PCR test results certification has been led separately by WHO, the European Union, and the World Economic Forum and the Commons Project in the past year (*47-49*).

Japan, being the host country of the G20 in 2019, is in place to take these lessons on unaddressed issues, to alert the international community and apply them to ensure effective UHC among the marginalized and vulnerable population. Given the circumstance of low priority on women and children in UHC strategies (*50*), G20 counties like Japan with a comparative advantage in information technology face a great amount of opportunity to collaboratively create new platforms and business models for digital health locally, regionally, and globally. This would lead to Japan and other G20 countries taking a further leadership role for UHC, in order to make sure that the UHC concept is adapted to every population and secures human rights for health. The enhanced leadership could be enforced by different key actors mentioned in this paper as well as by working with the private sector.

Leadership towards digitalization of disease comprehensive health records and its tracking mechanisms *via* data linkage of individual health records should be driven further not only by health authorities, but also among coordination with humanitarian and non-health authorities, including agencies such as United Nations High Commissioner for Refugees (UNHCR), United Nations Relief and Works Agency for Palestine Refugees in the Near East (UNRWA), or the International Organization for Migration (IOM). Health systems governance and financing require collaboration among multi-stakeholders that quickly respond to health emergencies and allow optimal allocation of existing budgets simultaneously, which could be facilitated by PPP, yet a good balance of input among other supporting actors. From the G20 Osaka, the UN-HLM on UHC (September 2019), and G20 Health Ministers' Meeting in Okayama (October 2019), and the 2nd UHC Forum in Bangkok (January – February 2020), among others, UHC has continued to be acknowledged and highlighted as a key health issue globally. Along with future G20 summits, forthcoming milestones beyond G20 Riyadh Leaders' Summit are nearing, including the G20 Rome Leaders' Summit in October 2021, along with consecutive large events planned in Tokyo during 2021 and beyond. For better global health governance, Japan's experiences in leading the 2019 G20 shows challenges and future opportunities to align the definitional disparities between various stakeholders to accelerate inclusive political momentum for UHC, and to ensure sustainable commitment towards UHC from both developed and developing nations. These lessons should be applied in the future G20 meetings, as the world leaders convene in Rome in October 2021 to discuss the health of the global community in the COVID-19 pandemic and post-pandemic worlds.

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REVIEW

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Effects of self-management interventions with behavior-change support on long-term adherence in patients with chronic respiratory diseases: A systematic review

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Abstract: The aim of this systematic review is to determine the effects of self-management interventions with behavior-change support on medication adherence and smoking cessation in patients with chronic respiratory disease. We also describe the theories of health behavior change and behavior change techniques (BCTs) used to design these interventions and their mode of delivery. The PubMed/MEDLINE, Cochrane Library, CINAHL, and Pedro databases were systematically searched for relevant articles published up to November 2021. Randomized controlled trials (RCTs) that evaluated the effect of self-management interventions with behavior change support on medication adherence, correct inhaler use, and smoking cessation were included. Effect sizes (odds ratios) with 95% confidence intervals were calculated and pooled for random-effect meta-analysis. Of 5,223 articles identified, 15 were RCTs that met the inclusion criteria for the meta-analysis. Five of these RCTs were based on behavior change theory, including social cognitive theory and a transtheoretical model. Between one and eight components of BCTs in Behavior Change Technique (BCT) Taxonomy version1 were included in all interventions. The most frequent BCT components were social support (emotional) (n = 8), instruction on how to perform the behavior (n = 8), and goal setting (behavior) (n = 7). Meta-analysis showed that self-management interventions with behavior change support have positive effects on medication adherence, correct inhaler use, and smoking cessation for more than 6 months after their implementation. This indicates that individually tailored self-management interventions with behavior change support are effective in improving long-term medication adherence and smoking cessation in patients with chronic respiratory disease.

***Keywords*:** behavior change theory, health science, behavior change techniques, self-care

Introduction

Medication adherence and smoking cessation are essential components of managing patients with chronic respiratory disease. According to the World Health Organization, adherence to long-term therapy is defined as the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyles changes – corresponds to agreed recommendations from a health care provider (*1*). However, adherence is influenced by social and economic factors, the characteristics of the disease, and patient-related factors (*1*). Adherence to medication is less than 50% in many patients with chronic obstructive lung disease (COPD) because of patient-related factors, which include depression and beliefs and concerns about medication (*2*). Lack of confidence in inhaler use is also associated with lower adherence in these patients (*3*).

It has been suggested that interventions based on behavior change theory are more effective in improving adherence in people with chronic respiratory disease (*4,5*). Since the 1990s, studies in Japan and overseas have reported that approaches for enhancing self-efficacy are effective in changing patients' behavior, and the use of these approaches became more widespread in the 2000s (*6*). The respiratory rehabilitation statement published in Japan in 2018 stated that education on self-management for patients with respiratory disease should support behavior change to promote and maintain health and increase adherence (*7*). COPD was one of the major chronic respiratory diseases highlighted in Health Japan 21 (second term) (*8*), and there is an increasing focus on the importance of preventing exacerbations and disease progression. However, there is limited information on the long-term effects of behavior change interventions based on behavioral science on medication

adherence and smoking cessation from meta-analysis of randomized controlled trials (RCTs). Moreover, there are limited data on the components of behavior change intervention that are effective.

This systematic review aimed to determine the long-term effects of self-management interventions with behavior change support on medication adherence and smoking cessation in patients with chronic respiratory disease by meta-analysis of RCTs. We also aimed to identify the extent to which behavior change theory and BCTs have been implemented, the mode of delivery used for the interventions (how: place of delivery, provider, delivery format) and the components of interventions (what). We also investigated the effects of correct inhaler use, which is another important component of medication adherence by meta-analysis.

Method

Protocol and objective

This systematic review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement (*9*) but was not registered in advance.

Literature search and study inclusion process

Search strategy and databases

The PubMed/MEDLINE, Cochrane Library, Cumulative Index to Nursing & Allied Health Literature (CINAHL), and Pedro databases were searched to identify relevant articles published up to November 2021. The search strategy was adapted to each database, and the search terms are shown in Table 1.

Inclusion criteria

RCTs (including feasibility and pilot studies) that evaluated the effects of self-management interventions supporting behavior change on medication adherence, correct inhaler use, and smoking cessation were sought. Medication adherence was assessed by the number of participants who were adherent. Correct inhaler use was assessed based on the number of participants who followed the steps for inhaling medication from the inhalation device correctly. Studies that reported medication adherence and smoking cessation were included even if these were not the primary outcomes.

The eligibility criteria were as follows: intervention that can be implemented at home with self-management; study participants aged 18 years or older; chronic respiratory disease diagnosed by a physician; implementation of a psychological or behavioral self-management intervention or mention of the term "behavior change", "health behavior" or "behavioral intervention"; outcome assessment at more than 6 months the start of intervention; and a full-text version published in English.

Exclusion criteria

Studies that targeted a combination of respiratory and non-respiratory diseases were excluded, as were those published as quasi-randomized trials, systematic reviews, letters, editorials, cross-sectional studies, and case reports.

Outcome measurements

Eligible studies from the literature search could use self-report or objective measurements for medication adherence, and self-report or biochemical verification for smoking cessation.

Data extraction

Three reviewers (JN, AT, MF) independently screened titles and retrieved abstracts to identify studies that met the inclusion criteria. Full-text screening was performed for studies that could not be confidently excluded. The full texts of potentially eligible studies were retrieved and assessed for eligibility by one reviewer (MF). Disagreements and questions were resolved by consensus at discussion meetings attended by all reviewers.

The individual components of the behavior change intervention described in the included studies were extracted and classified in accordance with the BCT Taxonomy version 1 (BCTTv1) (*10,11*), which was developed to identify individual components of behavior change interventions and enable accurate reporting and replication of content.

Table 1. Search terms used in electronic database search

PICs component	Search terms
Patient	"chronic respiratory disease", "chronic respiratory failure", "Respiratory Tract Disease", "Respiratory Tract Disorder", "Respiratory Disease", "Lung Disease", "Chronic Lung Disease", "Pulmonary Disease"
Intervention	"behavior therap*", "behaviour therap*", "behavior change", "behaviour change", "behavior modification", "behaviour modification", "behavior intervention", "behaviour intervention", "behavioral intervention", "self manag*", self-management, self-care, self-car*, self-report*, home-based, home
Comparison	trial, randomized, RCT

*the wildcard character.

Quality assessment

The quality of the studies was assessed using the Cochrane Collaboration's tool for assessing the risk of bias (version 2.0). This tool includes five or six domains of bias depending on the method used for randomization. Five domains are used for parallel-group trials in which study participants are individually randomized: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. A sixth domain, namely, bias arising from the timing of identification and recruitment of participants, is added for cluster-randomized trials. The risk of bias was assessed by two authors (YT, MF) working independently. Any disagreements were resolved by discussion; if a decision could not be reached, a final decision was made at a consensus meeting attended by all the authors.

Statistical analysis

All statistical analyses were performed using Review Manager (RevMan) version 5.4. (*12*). Odds ratio (OR) were calculated along with their 95% confidence intervals (CIs). Assuming a degree of heterogeneity between the interventions, the data were pooled using a random-effects model. Statistical heterogeneity between study outcomes was assessed using the I^2 statistic according to the method outlined by Higgins *et al.* (*13*). I^2 values of 25%, 50%, and 75% are considered to indicate low, moderate, and high heterogeneity, respectively (*13*). In the case of high heterogeneity (I^2 > 75%), a subgroup analysis was performed to identify any valid causes. A sensitivity analysis was conducted if necessary.

Results

Study selection

The literature search up to November 2021 identified 9,528 records, 4,305 of which were found to be duplicates and were excluded. After screening of titles and abstracts, 5,031 studies were excluded, leaving 192 for full-text review. From the results of the review, 158 studies were excluded based on the eligibility criteria and 19 were excluded because their data were reported in an inappropriate format. Finally, data could be extracted from 15 studies that met the eligibility criteria. The outcome of the search process and study selection is shown in Figure 1.

Study characteristics

Overview of studies

The characteristics of the 15 studies are summarized in Table 2. All the studies were published between 2004 and 2021. Two studies each were performed in China (*14,15*), Israel (*16,17*), the Netherlands (*18,19*), and the UK (*20,21*); one study each was performed in Australia (*22*), Denmark (*23*), Iran (*24*), Jordan (*25*), Spain (*26*),

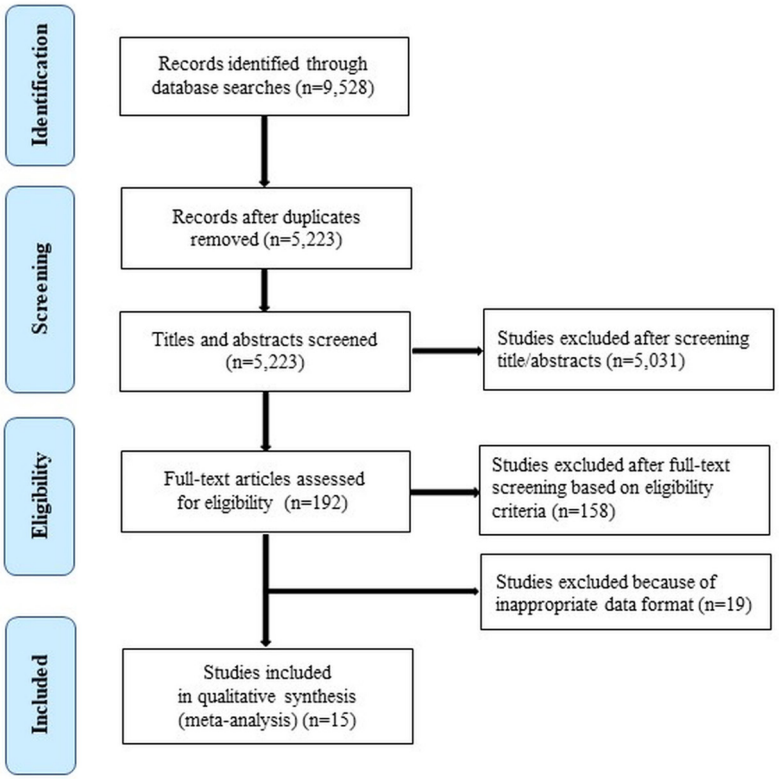

Figure 1. PRISMA flow-diagram of the study selection process.

Table 2. Characteristics of studies included

Author, year (*Ref.*)	Participants (illness, lung function, sex, age)	Comparison	Intervention Component, delivery place, who delivered	Theory	Outcome/ measurement	End point
Borglykke *et al.*, 2008 (*23*)	COPD (admitted with acute exacerbation) FEV_1 %: - Male: Ex 35%, Con 36% Mean Age: Ex 65, Con 67	Control: Received standard information on the benefits of smoking	Smoking cessation groups (SCG): Weekly 2-h sessions over 5 weeks, three sessions after the quitting date, follow-up session after 3 months Hospitalized setting; nurses	Not described	Smoking cessation rate/ Self-report and carboxyhemoglobin	1Y
Garcia-Aymerich *et al.*, 2007 (*26*)	COPD FEV_1 1.2 ± 0.5L Male 86 %, Age 73 ± 8	Usual care: Pharmacological prescriptions and treatment followed the standard protocols of the center	Integrated care (IC): A 2-h educational session at discharge, individually tailored care plan (visit patient's home within 72 h after discharge, weekly phone calls during the first month after discharge, and one phone call at 3 and 9 months after discharge), access through an ICT[*2] platform Primary care setting and home; physician, nurse, social worker	Not described	Medication adherence scale, Inhaler Adherence Scale, observed skills for administration of inhaled drugs	12M
Hesselink *et al.*, 2004 (*18*)	Asthma, COPD or mixed Pre-FEV_1 % predicted: Ex 81.9 ± 22.6 Con 84.7 ± 23.4 Male: Ex 35%, Con 28% Age: Ex 49.9 ± 14.2, Con 44.7 ± 13.6	Usual care: Continued to receive usual-care from GPs	Education program: One to four 30-min semi-structured consultations (giving information, individual training regarding inhalation technique, discussion about barriers in coping with the disease, a supportive smoking cessation program, advice about when to consult a doctor, provide free booklets) Primary care setting; general practice assistants	Not described	Inhalation technique/ checklist developed by the Dutch Asthma Foundation, medication use/three-item checklist	2Y
Hilberink *et al.*, 2005 (*19*)	COPD FEV_1 %: - Male: Ex 46.3%, Con 55.4% Age: Ex 58.0 ± 12.1, Con 60.1 ± 11.5	Usual care: (Not described in detail)	Smoking Cessation in patients with COPD (SMOCC): A 4-h group training session, outreach visits and telephone calls depending on the motivational stage, delivering support materials General practices and home; GP and nurses	Trans theoretical model/	Point prevalence/ self-report and biochemical analysis	6M
Jarab *et al.*, 2012 (*25*)	COPD FEV_1 predicted (%) Ex 53.7 ± 15.9, Con 52.8 ± 17.8 Male: Ex 39.4%, Con 41.8% Age (median, IQR): Ex 61(14), Con 64(15)	Control group: (Not described in detail)	Pharmaceutical care program: Intensive education (no repeated process) making a medication table, discussion about the importance of exercise, symptom control and techniques for expectoration, providing a booklet Outpatient clinic; pharmacist	Not described	Medication adherence (Morisky Scale)/ self-report	6M
Jolly *et al.*, 2018 (*20*)	COPD meanFEV_1 predicted (%): 71.6% Male: EX 63%, Con 64% Mean Age: Ex 70.7 ± 8.8, Con 70.2 ± 7.8	Usual care: Received a standard information leaflet about self- management of COPD	Telephone health coaching intervention: Telephone coaching session for 35-60 min, 15-20 min telephone sessions at weeks 3, 7, and 11, providing standard written prompts or information at weeks 16 and 24 Home; Nurses	Social Cognitive Theory	Attempted to quit smoking in past 6 month/ self-report	12M

Abbreviations: Ex, experimental; Con, control; COPD, chronic obstructive pulmonary disease; ICT = information and communication technologies; NRT, nicotine replacement therapy; SPACE, Self-Management Program of Activity, Coping and Education; Y = years; M = months.

Table 2. Characteristics of studies included (continued)

Author, year (*Ref.*)	Participants (illness, lung function, sex, age)	Comparison	Intervention Component, delivery place, who delivered	Theory	Outcome/ measurement	End point
Kalter-Leibovici *et al.*, 2018 (*17*)	COPD FEV_1% predicted Ex 43.8 ± 10.8 Con 44.1 ± 10.0 Male: Ex 69.0%, Con 73.3% Age: Ex 66.7 ± 9.9 Con 68.3 ± 10.0	Recommended care alone: Received selfcare education, follow-up by pulmonologists, treatment with medication and oxygen, dietary advice, psychosocial support, smoking cessation group sessions and prescriptions for smoking cessation medications, physical exercise sessions	Recommended care plus disease management Disease management: Face-to-face sessions during patients' visits, remote contacts between visits, monitoring disease signs and symptoms, educational sessions for caregivers Community-based COPD centers; pulmonologists and nurses	Not described	Quit smoking/ patients' reports	3Y
Kessler *et al.*, 2018 (*28*)	COPD FEV_1% predicted Ex 37.8 ± 12.4, Con 36.4 ± 12.3 Male: Ex 69.4%, Con69.8% Age: Ex 67.3 ± 8.9, Con 66.6 ± 9.6	Received the usual or routine COPD care	Multicomponent home-based disease management intervention (COMET): Four individual home sessions over 5 weeks, monthly group or individual telephone sessions for 12-24 months, home monitoring at least once per week, an e-health telephone/web platform. Home; case managers and hospital physician	Not described	Smoking habits/ measurement: not described in detail	12M
Khdour *et al.*, 2020 (*16*)	Asthma FEV_1%: Ex 72.4 ± 15.2, Con 69.2 ± 14.4 Male: Ex 43.2%, Con 38.6% Age >60: Ex 25.2%, Con 21.6%	Usual care: Arranged by the hospital without any structured interventions	Pharmaceutical care in asthma management: Adherence assessment and education on an individual basis, inhaler techniques training, follow-up telephone calls, provide action plans, written medication lists and an asthma manual booklet Outpatient clinic and home; Pharmacist	Concern and beliefs	Medication adherence/ Morisky Scale, Inhaler technique/Standardized checklists	12M
Liang *et al.*, 2019 (*22*)	COPD FEV_1% predicted Ex 69.0 ± 20.5, Con 70.8 ± 19.3 Male: Ex 60.5%, Con 62.6% Age: Ex 66.6 ± 10.8 Con 61.7 ± 10.1	Usual care: Continued to provide routine care, given the Lung Foundation Australia booklet. Quitline referral was provided to smokers.	Interdisciplinary primary care: Individualized smoking cessation support consisted of brief counseling and "quitline" referral, prescription medications for smoking cessation, interview at home by pharmacist, education focusing on medication use, an 8-week home-based pulmonary rehabilitation consisting of one home visit and weekly follow-up telephone calls. General practitioners, clinic staff, pharmacist, physiotherapist	Not described	7-day point prevalence smoking abstinence/ biochemical analysis	6M
Lou *et al.*, 2013 (*14*)	COPD FEV_1%: - Male: Ex 48%, Con 48% Age: Ex 61.6 ± 10.2 Con 61.5 ± 10.1	Usual care: Treated in the usual manner	Behavioral intervention program: Brief smoking cessation advice and discussion for 5-8 min, home visits at least once a week, follow-up once a week during the first month and once a month until the end of the study, providing a booklet Healthcare centers and home; general practitioners	Not described	Continuous smoking abstinence rates/ Self-report and expired carbon monoxide level	4Y

Abbreviations: Ex, experimental; Con, control; COPD, chronic obstructive pulmonary disease; ICT = information and communication technologies; NRT, nicotine replacement therapy; SPACE, Self-Management Program of Activity, Coping and Education; Y = years; M = months.

Table 2. Characteristics of studies included (continued)

Author, year (*Ref.*)	Participants (illness, lung function, sex, age)	Comparison	Intervention Component, delivery place, who delivered	Theory	Outcome/ measurement	End point
Mitchell *et al.*, 2014 (*21*)	COPD FEV_1 % predicted Ex 56.04 ± 16.76, Con 59.60 ± 17.42 Male: Ex 60.6%, Con 49.4% Age: Ex 69 ± 8.0, Con 69 ± 10.1	Usual care: (Not described in detail)	SPACE for COPD: Work with SPACE for COPD manual over 6 weeks, a 30-45 min consultation, telephone calls at 2 and 4 weeks Primary care settings and home; physiotherapist	Readiness to change	Smoking status/ Self-report	6M
Sharifpour *et al.*, 2020 (*24*)	COPD FEV_1 act: Ex 1.91 ± 0.7, Con 1.94 ± 0.74 Male: 100% Age: Ex 54 ± 8, Con 56 ± 10	NRT	Guided self change + NRT: Five 1-h sessions over 5 weeks, including individual counseling, NRT, telephone follow ups Hospital and home; psychotherapist	Trans theoretical model	Smoking abstinence/ self-report	29W
Wang *et al.*, 2021 (*15*)	COPD FEV_1 % predicted Ex 43.7 ± 13.2, Con 45.4 ± 11.5 Male: Ex 66.7 %, Con 74.4% Age: Ex 63.2 ± 7.5, Con 64.4 ± 7.0	Control group: Received routine care, which included health education	Mobile health application program: Knowledge and information support, visual aids to teach participants skills to manage the disease, motivational support (Not described in detail)	Not described	Smoking abstinence/ self-report	12M
Willard-Grace *et al.*, 2020 (*27*)	COPD FEV_1 % predicted: 58 ± 20 Male: 65.5% Age: 61.3 ± 7.6	Usual care: Received resources provided by their clinic	Health coaching intervention: Accompanied to visits with clinicians, met individually in the community or at their home, telephone calls at least once every three weeks Primary care setting and home; health coaches, pulmonary specialists	Not described	Medication adherence/ patient-report, inhaler use/ observation and checklist	9M

Abbreviations: Ex, experimental; Con, control; COPD, chronic obstructive pulmonary disease; ICT = information and communication technologies; NRT, nicotine replacement therapy; SPACE, Self-Management Program of Activity, Coping and Education; Y = years; M = months.

and the US (*27*); and one study was a collaboration of European countries (France, Germany, Italy, and Spain) (*28*). The period between the start of the intervention and the final follow-up ranged from 6 to 48 months. The interventions were delivered by various health-related occupations.

Most commonly, in 12 studies, the intervention was conducted on an individual basis from the start of the intervention or was group-based with follow-up on an individual basis (*14,15,16,18-22,24,26-28*), and follow-up was carried out by telephone in 10 studies (*15,16,19,20-22,24,26-28*). One of these studies also used information and communications technology and a web platform (*28*).

Illness and severity

The most common respiratory disease was COPD (*14,15,17,19-28*) followed by asthma (*16,18*), and mixed COPD-asthma (*18*) (Table 2). Five of the 11 studies targeting patients with COPD (*17,20,21,27,28*) described the severity of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline (*29*), which was used as the basis for the Guideline for the Management of Chronic Obstructive Pulmonary Disease published by the Japanese Respiratory Society (*30*). The study by Jolly *et al.* (*20*) targeted patients with mild-to-moderate COPD. Mitchell *et al.* (*21*) included all stages of COPD, with the majority (60.3%) of patients classified as having moderate disease. Kalter-Leibovici *et al.* (*17*) and Kessler *et al.* (*28*) only included patients with severe COPD; severe exacerbations were also included in the study by Kessler *et al.* (*28*). The study by Willard-Grace *et al.* (*27*) targeted patients with moderate-to-severe COPD. The remaining seven studies (*14,19,22-26*) did not use the GOLD classification. Three of the studies, namely those by Garcia-Aymerich *et al.* (*26*), Borglykke *et al.* (*23*), and Wang *et al.* (*15*), included patients admitted with symptoms of acute exacerbation; the remaining four studies did not report the criteria used to determine severity.

Assessment of outcomes

The measurement methods used are summarized in Table 2.

Medication adherence was assessed by a questionnaire in three studies (*16,25,26*), a standardized checklist in one study (*18*), and by direct interview in another study (*27*). For the purposes of this review, the authors extracted the number of patients who were reported as adherent with medication from each study.

Correct inhaler use was evaluated by observation using a checklist in two studies *(16,27)* and by observation only in one study (*26*). Data for another study (*20*) that reported the number of participants who received an inhaler check followed by recommendations was also included in the meta-analysis.

Smoking status and abstinence rates were measured by self-report in nine studies, four of which also included biochemical verification (*14,19,22,23*). Only two of these studies defined smoking cessation (*i.e.*, abstinence from cigarettes during the previous 7 days) *(19,22)*.

Quality assessment

The results of the quality assessment using the Cochrane risk of bias tool are shown in Figure 2. An individually parallel randomized tool was used in 12 studies and a cluster parallel randomized tool was used in three studies. The most common types of bias identified were

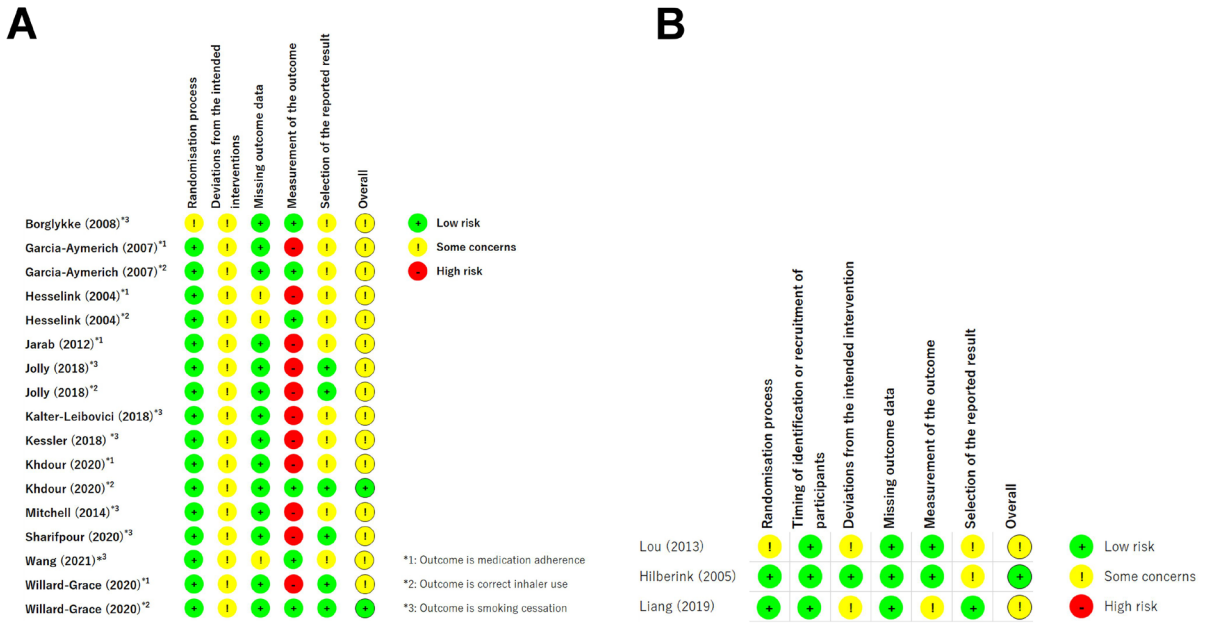

Figure 2. Risk of bias of individual domains across included randomized trials. (A) Individually randomized trials; (B) Cluster-randomized trials.

bias due to deviations from intended interventions, bias in measurement of the outcome, and bias in selection of the reported result. All methods used to measure medication adherence and most of those used to measure smoking cessation adherence were based on self-reported questionnaires. This is one of the limitations of this review. However, bias arising from deviations from intended interventions was unavoidable because all study participants would have been aware of their assigned intervention during the trial. Bias in terms of selection of the reported result reflects the fact that most of the details concerning the research protocols used were not available.

Behavior change theories or techniques used in self-management interventions

One study used social cognitive theory (*20*), three used a transtheoretical model that included readiness to change (*19,21,24*), and one mentioned consideration of participants' concerns and beliefs but did not report application of a specific theory (*16*) (Table 2). Ten studies did not mention behavior change theory.

Between one and eight BCTs categorized with reference to BCTTv1 were included in all interventions (Table 3). Overall, the most frequent BCT components were social support (emotional) (n = 8), instruction on how to perform the behavior (n = 8), and goal setting (behavior) (n = 7).

The most frequent components for promoting behavior change and adherence with medication were instruction on how to perform the behavior (n = 5) (*16,18,20,26,27*), followed by goal setting (behavior) (n = 3) (*16,20,27*) and problem solving (n = 3) (*18,20,27*).

For smoking cessation, social support (emotional) (n = 6) (*14,15,17,21,22,24*) was used most frequently, followed by goal setting (behavior) (n = 5) (*14,19,20,23,24*) and pharmacological support (n = 5) (*17,19,22-24*). Of the five studies that used pharmacological support, two also included this component for the purposes of comparison between groups (*17,24*).

Effects of self-management based on behavior change interventions to promote adherence

i) Smoking cessation

Ten studies were included in a random-effects meta-analysis (*14,15,17,19-24,28*). These studies included 5,406 patients with COPD (intervention groups, n = 2,838; control groups, n = 2,568). In four studies (*14,19,23,24*), all participants were smokers at baseline and received self-management intervention specifically for smoking cessation. In the other six studies (*15,17,20-22,28*), not all participants were smokers; in these studies, smoking cessation was included as part of a multicomponent intervention and the only data provided for smoking cessation was for patients who were smokers at baseline. Meta-analysis revealed that the number of participants who quit smoking was significantly higher in the intervention group than in the control group (OR: 2.91, 95% CI: 1.20-7.06, p = 0.02; Figure 3).

The statistical heterogeneity was high (I^2 = 92%) and was explored by sensitivity and subgroup analyses. The sensitivity analysis was performed by removing each study one by one and confirmed that the result was not markedly affected by any single study. Subgroup analyses were conducted to separate studies according to severity of illness, differences in components of the intervention, outcome measurements, and duration of follow-up. When the studies were grouped by severity of illness, there was a distinction between studies that included patients with severe or exacerbated COPD (15,17,23,28) and those that included all stages of COPD (14,19-22,24). The sub-group analyses showed that the intervention improved adherence to smoking cessation among only participants with severe or exacerbated COPD (OR: 2.57, 95% CI: 1.54-4.28, p = 0.0003; Figure 4). Other subgroup analyses did not significantly change the heterogeneity.

ii) Medication adherence

Five studies were subjected to random-effects meta-analysis (*16,18,26,27*). These studies included 725 participants (intervention groups, n = 353; control groups, n = 372).

Pharmacological support was the only intervention in three studies (*16,25,27*) and part of a multicomponent intervention in two studies (*18,26*).

Meta-analysis showed that the number of adherent participants was higher in the intervention group than in the control group (OR: 2.27, 95% CI: 1.57-3.27, p < 0.0001; Figure 5). The statistical heterogeneity was low (I^2 = 0%).

iii) Correct inhaler use

Five studies were included in a random-effects meta-analysis (*16,18,20,26,27*). These studies included 1,104 participants (intervention groups, n = 533; control groups, n = 571). The meta-analysis showed that the number of participants who used their inhalers correctly was higher in the intervention group than in the control group (OR: 4.07, 95% CI: 1.66-9.96, p = 0.002; Figure 6). The statistical heterogeneity was high (I^2 = 88%) and explored by sensitivity and subgroup analyses. A sensitivity analysis, which was conducted by removing a study one by one showed that the result was not markedly affected by any single study. Subgroup analysis according to type and severity of disease did not change the I^2 value.

Discussion

Previous systematic reviews in patients with chronic respiratory diseases have shown that behavior change support is effective in improving adherence (*4,31*). However, the present systematic review is the first

Table 3. Frequency of behavior change techniques identified in trials

Author, year (*Ref.*)	1. Goals and planning	2. Feedback and monitoring	3. Social support	4. Shaping knowledge	5. Natural consequences	11. Regulation	12. Antecedents
Borglykke *et al.*, 2008 (*23*)	1.1. Goal setting (behavior)		3.1. Social support (unspecified)			11.1. Pharmacological support	
Garcia-Aymerich *et al.*, 2007 (*26*)	1.4. Action planning			4.1. Instruction on how to perform the behavior			
Hesselink *et al.*, 2004 (*18*)	1.2. Problem solving	2.5. Monitoring of outcomes of behavior without feedback		4.1. Instruction on how to perform the behavior			
Hilberink *et al.*, 2005 (*19*)	1.1. Goal setting (behavior) 1.2. Problem solving				5.1. Information about health consequences	11.1. Pharmacological support	
Jarab *et al.*, 2012 (*25*)			3.3. Social support (emotional)				
Jolly *et al.*, 2018 (*20*)	1.1. Goal setting (behavior) 1.2. Problem solving 1.5. review behavior goal	2.2. Feedback on behavior 2.3. Self-monitoring of behavior		4.1. Instruction on how to perform the behavior			
Kalter-Leibovici *et al.*, 2018 (*17*)	1.4. Action planning	2.1. Monitoring of behavior by others without feedback 2.7. Feedback on outcomes of behavior	3.3. social support (emotional)			11.1. Pharmacological support	
Kessler *et al.*, 2018 (*28*)	1.3. Goal setting (outcome) 1.4. Action planning	2.6. Biofeedback					
Khdour *et al.*, 2020 (*16*)	1.1. Goal setting (behavior) 1.4. Action planning		3.3. Social support (emotional)	4.1. Instruction on how to perform the behavior			
Liang *et al.*, 2019 (*22*)			3.3. Social support (emotional)	4.1. Instruction on how to perform the behavior		11.1. Pharmacological support	
Lou *et al.*, 2013 (*14*)	1.1. Goal setting (behavior)	2.1. Monitoring of behavior by others without feedback 2.6. Bio feedback	3.1. Social support (unspecified) 3.3. Social support (emotional)		5.1. Information about health consequences 5.2. Salience of consequences		12.4. Distraction
Mitchell *et al.*, 2014 (*21*)	1.4. Action planning	2.3. Self-monitoring of behavior	3.3. Social support (emotional)	4.1. Instruction on how to perform the behavior			
Sharifpour *et al.*, 2020 (*24*)	1.1. Goal setting (behavior) 1.2. Problem solving	2.2. Feedback on behavior 2.3. Self-monitoring of behavior	3.3. Social support (emotional)		5.4. Monitoring of emotional consequences	11.1. Pharmacological support	
Wang *et al.*, 2021 (*15*)			3.3. Social support (emotional)	4.1. Instruction on how to perform the behavior			
Willard-Grace *et al.*, 2020 (*27*)	1.1. Goal setting (behavior) 1.2. Problem solving	2.2. Feedback on behavior		4.1. Instruction on how to perform the behavior			

The numbers are classification numbers of BcTTv1.

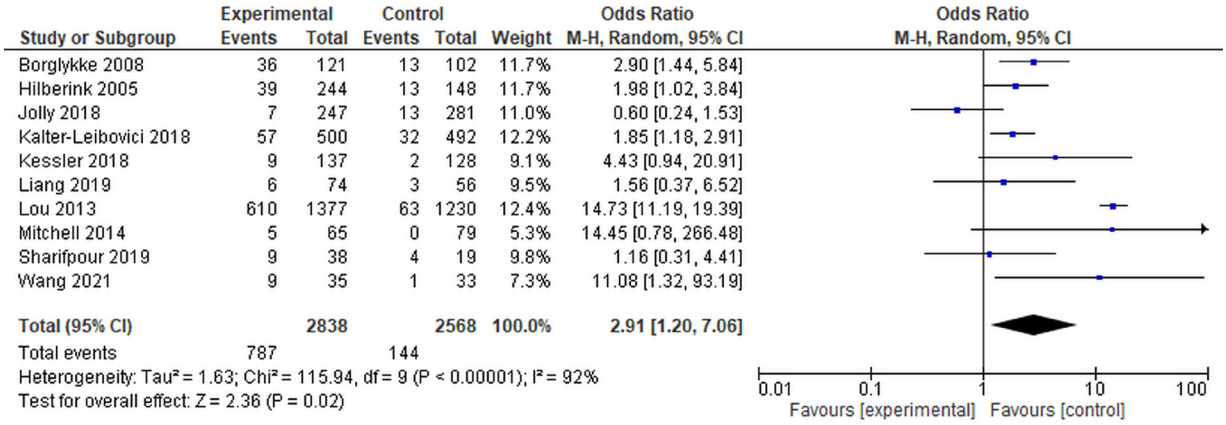

Figure 3. Meta-analysis to estimate the effect of self-management interventions with behavior support on smoking cessation.

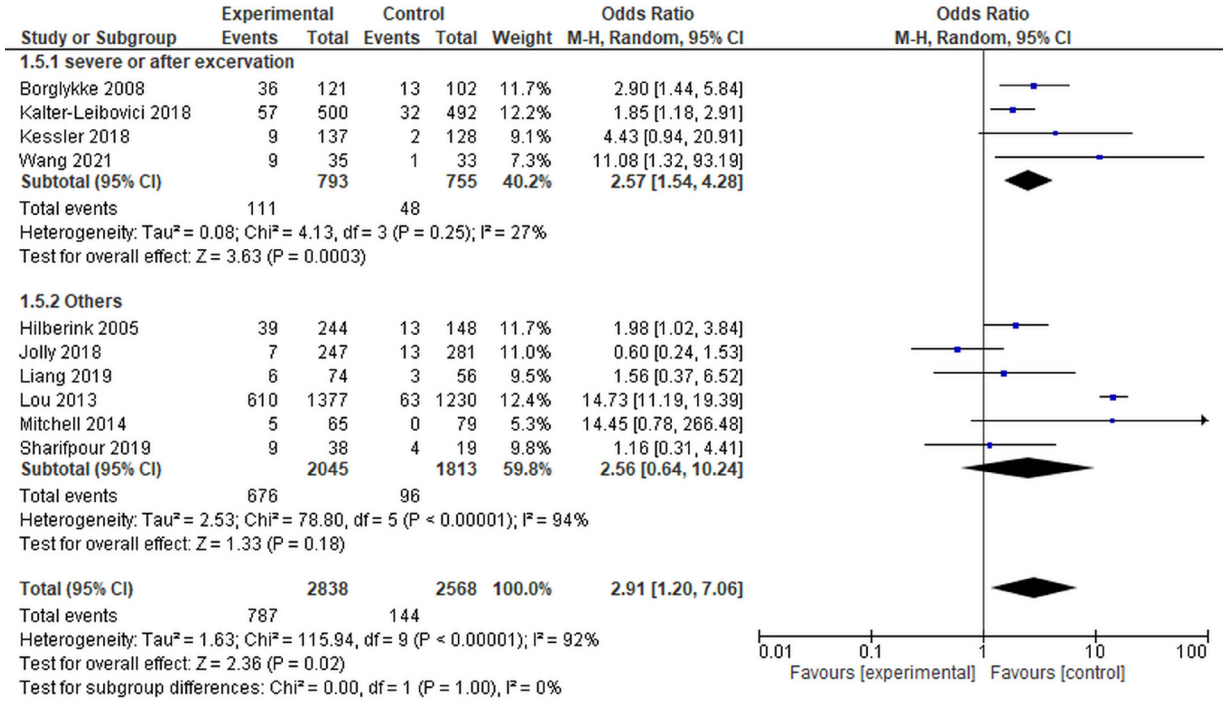

Figure 4. Sub-group analysis of smoking cessation grouped by severity of illness.

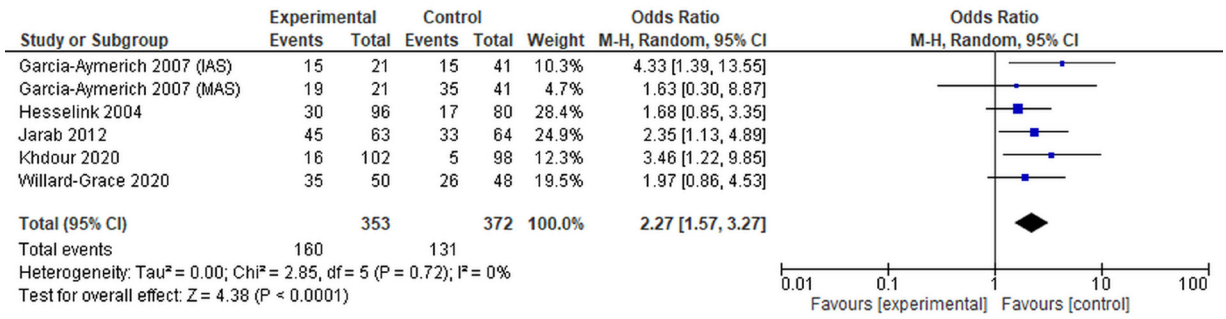

Figure 5. Meta-analysis to estimate the effect of self-management interventions with behavior support on medication adherence.

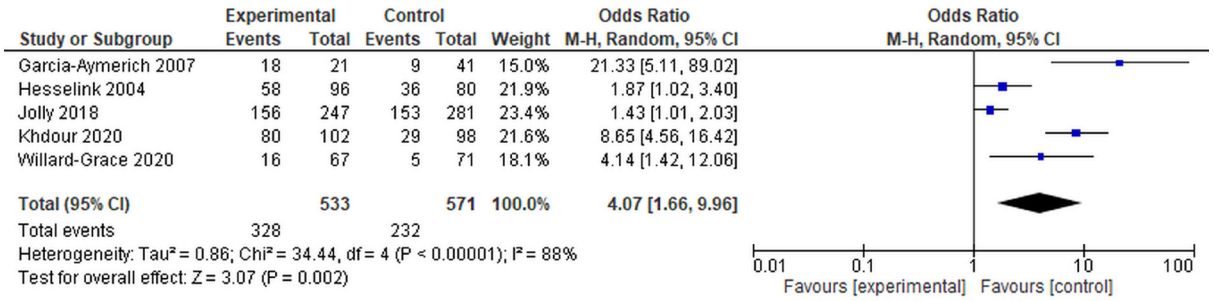

Figure 6. Meta-analysis to estimate the effect of self-management interventions with behavior support on correct inhaler use.

to examine the long-term effects of self-management interventions with behavior change support to improve medication adherence, smoking cessation, and correct inhaler use in patients with chronic respiratory disease. It is also the first aiming to classify the contents of interventions by behavior change technique (BcTTv1). All three components are essential for these patients to be able to manage their disease. Our findings suggest that interventions with behavior change support achieve better rates of medication adherence and smoking cessation than interventions without behavior support and that these effects can persist for at least 6 months after implementation. According to the transtheoretical model of health behavior change, the maintenance stage is estimated to last from 6 months to about 5 years (*32*), which suggests the importance of supporting the transition to the maintenance stage in patients with chronic disease.

As reported elsewhere (*4*), many of the studies included in our meta-analysis were not based on behavior change theories for the development of the interventions and none of the interventions were developed based on BCTs. Several BCTs included in intervention strategies were extracted by referring to the BCTTv1 (Table 3).

For smoking cessation, social support (emotional) (n = 6) (*14,15,17,21,22,24*) was used most frequently, followed by goal setting (behavior) (n = 5) (*14,19,20,23,24*) and pharmacological support (n = 5) (*17,19,22-24*). Emotional support such as motivational interviews may be important when self-efficacy is diminished by chronic illness. There have been reports of code classifications being devised for effective BCTs that suggest behavioral support accompanied by BCTs contributes to smoking cessation (*33,34*). Goal setting (behavior), pharmacological support, and information about health consequences have been reported to be the most promising BCTs for maintaining smoking cessation after leaving a smoking cessation facility (*34*), which is in line with our findings.

When subgroup analysis was performed, heterogeneity (I^2) was reduced when studies were divided according to severity of COPD (degree of airflow obstruction and acute exacerbation). Therefore, behavior change interventions may be more effective in patients with more severe airflow obstruction and in those who have experienced acute exacerbation of COPD. However, some reports suggest an association between the FEV_1/FVC and the likelihood of successful smoking cessation in patients with COPD (*35*), while other researchers have found no association between the severity of airflow obstruction and the effect of pharmacological treatment on smoking cessation (*5*). However, given the small number of studies included in this review, further investigations are needed.

Interventions with behavior support were more likely to achieve optimal long-term medication adherence and correct inhaler use than those that did not include behavior support. Subgroup analysis did not alter the high heterogeneity (I^2) of the results for correct inhaler use. This can be attributed to the small number of studies and the different measurement methods used in the studies. However, all studies found differences in outcomes between the intervention and control groups, suggesting that the intervention improved adherence. Although there has been limited research on supporting medication adherence with BCTs, there has been a study in which 11 theory-based BCTs was selected to improve medication adherence in older adults (*36*), and the importance of taking into account each patient's individual needs and adopting a tailored approach to delivery of BCTs has been noted (*37*).

With the exception of one study, all interventions adopted repeated processes and patients in the intervention groups were followed up remotely by telephone or *via* a website platform. The components of the interventions were tailored individually according to each patient's specific needs. The previous study reported that person-centered support *via* telephone can mitigate worsening self-efficacy in patients with COPD by supporting and strengthening their ability and self-esteem (*38*). Our analysis suggests that individually tailored self-management interventions with health behavior change support were effective in improving medication adherence and smoking cessation. However, our review may contain a degree of bias toward BCTs that are easier to provide remotely. Various remote devices have been developed in recent years, so further research is needed to confirm the elements of an

intervention that support self-management of patients with chronic respiratory disease.

This review has several limitations. First, none of the intervention strategies was developed in accordance with the BCTTv1. We did not contact any authors to obtain unpublished data, so we could not extract information on behavior change theories that were not explicitly stated but may have been used, and it was also difficult to code and classify the components of BCTs according to the authors' intentions. Furthermore, it was not possible to classify the BCTs used in the control groups because too little detail was provided. Second, medication adherence and smoking cessation were assessed by self-report, which may have introduced a degree of reporting bias. Only one study provided a definition of smoking cessation and not all studies reported the duration of abstinence from smoking. Moreover, although we included the number of participants reported to be adherent with medication in each study in our meta-analysis, the assessment criteria varied from study to study and may have influenced our results. Third, we included studies with a duration of at least 6 months from the implementation of interventions and analyzed the data measured at the final follow-up, so the measurement timing may have affected adherence. Fourth, although this review did not impose limits on the types of respiratory disease that could be included, most of the studies targeted patients with COPD. Therefore, our findings may be biased towards the characteristics of this patient population.

Conclusion

This review and meta-analysis demonstrated that self-management interventions with behavior change support improve adherence to smoking cessation, medication, and correct inhaler use and that the improvements can be maintained for at least 6 months in patients with chronic respiratory disease.

When tailored to the patient's specific needs, behavior change support is suggested to promote patient's self-management and improve long-term adherence.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Knowledge and practice for cervical cancer among female primary school teachers in Phnom Penh, Cambodia: A cross-sectional phone-based survey

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Abstract: Cervical cancer is a cancer with evidence-based and cost-effective preventive measures; Human Papilloma Virus (HPV) vaccination for school girls and cancer screening for women. In Cambodia, cervical cancer accounts for an estimated 11.4% and 10.4% of women's cancer and deaths in 2020, respectively. This study aimed to identify the knowledge of cervical cancer, its information sources, and the experiences of cervical cancer screening among female primary school teachers, who are key influencers of HPV vaccination. A cross-sectional study was conducted using telephone interviews with 100 female primary school teachers in Phnom Penh, the capital of Cambodia. All 100 participants had heard of cervical cancer, 94 (94%) had heard of screening, and 49 (49%) had ever undergone a screening. When asked about their knowledge regarding cause(s), symptom(s), detection, and treatment(s) of cervical cancer, 31%, 44%, 35%, and 55% respondents said "Do not know". Those who did not reply "Do not know" were asked open-ended questions. Many of their answers were judged as “incorrect” by gynecologists. Consequently only 1%, 38%, 63% and 28% of respondents replied with at least one correct answer regarding cause(s), symptom(s), detection and treatment(s) respectively. The most common sources of information were family and friends, followed by doctors, television, and the Internet. Among female primary school teachers with an above-average educational level, their knowledge of cervical cancer was generally low. To promote cervical cancer prevention, it is necessary to provide correct knowledge in a broad and accessible manner through involvement of local medical doctors and healthcare providers.

***Keywords*:** cervical cancer, screening, knowledge, attitude and practice, Cambodia

Introduction

Cervical cancer is a common public health problem worldwide, ranking as the fourth most common cancer among women (*1*). The highest incidence and mortality rates for cervical cancer are consistently observed in low- and middle-income countries (LMICs), where the majority of women are never screened for the disease (*1-3*). Without an urgent scale-up of services, the cervical cancer burden will increase to almost 460,000 deaths by 2040 in LMICs (*2*). Fortunately, cervical cancer is a cancer with evidence-based and cost-effective preventive measures. These include human papillomavirus (HPV) vaccination for girls as primary prevention and cervical cancer screening for women linked to treatment in the early stage as secondary prevention. Cervical cancer can be avoided in the future through implementing these measures (*4,5*). In many LMIC countries, where these preventive measures are not available, women have little knowledge of cervical cancer and its preventive measures (*6-11*). To promote screening among women to prevent cervical cancer, their own knowledge and understanding of cervical cancer are essential.

In Cambodia, one of the LMICs in South-east Asia, 5.93 million women aged 15 years and older are at risk for cervical cancer (*12*). In 2020, the number of cervical cancer incidences and mortality were estimated to be 1,135 and 634, accounting for 11.4% and 10.4% of female cancers, respectively (*1*). If no progress is made in cervical cancer prevention, the number of incidences and mortality are expected to increase by 1,790 (1.6-fold) and 1,090 (1.7-fold), respectively, 20 years after 2020. (*1*). The Ministry of Health of Cambodia

considers cervical cancer to be one of the most important health issues and has attempted to establish a screening program since 2007 (*13*) in addition to preparing for HPV vaccination in 9-year-old school girls (*13-16*). However, according to the 2016 STEP survey, only 11.3% of Cambodian women aged 18-69 years have ever been screened, indicating that cervical cancer screening is not yet widespread (*17*). Although the knowledge and understanding of the target women are essential to encourage them to undergo cervical cancer screening, there is limited information regarding knowledge and practice concerning cervical cancer among women in Cambodia (*10,18,19*). Since HPV vaccination is planned to be introduced as a routine immunization to 9-year-old girls in primary schools in 2023, primary school teachers are considered key influencers to school children and their parents who make a decision for vaccination (*20*). Promoting the understanding of cervical cancer among primary school teachers is indispensable to increase the acceptance and uptake of the vaccine by children and their parents. When female school teachers properly understand the importance of screening, it would also contribute to increase the administration of cervical cancer screening. Because of the above reasons, female primary school teachers were chosen as a target population.

This study aimed to identify the knowledge of cervical cancer, its information sources, and the experience of cervical cancer screening among female primary school teachers in Phnom Penh, Cambodia.

Methods

Study design

A cross-sectional phone-based survey was conducted in July 2020 among a sample of primary school teachers in Phnom Penh, the capital of Cambodia. The survey was initially designed to be conducted through face-to-face interviews at schools; however, it was changed to a phone-based interview because schools were closed and meetings and travel were restricted due to COVID-19.

Study population, sample size, and sampling

Our study was comprised of female teachers aged over 30 years (*i.e.*, the target age of cervical cancer screening based on the Cambodian national operational standard for cervical cancer screening (*16*) currently working in primary schools in Phnom Penh. Prior to conducting this study, full approval and cooperation were obtained from the Ministry of Education Youth and Sports, Cambodia, and Phnom Penh Municipality Department of Education Youth and Sports. Based on the agreement, the latest list of public primary schools and in-service teachers with their personal phone numbers was provided. In Phnom Penh, there were 158 public primary schools with 4,116 teachers, including 2,944 women. For the 2,944 study participants, the appropriate sample size was calculated to be 100, with a confidence interval of 95% and a standard error of 10%. In total, 100 study participants were recruited from randomly selected primary schools in four urban and four peri-urban districts of Phnom Penh.

Data collection method and instrument

To conduct the interviews, a structured questionnaire was developed, which consisted of demographic information, knowledge of cervical cancer, sources of information, and experience of cervical cancer screening.

For knowledge, the participants were asked about the cause, symptoms, detection, and treatment of cervical cancer. The participants were asked if they knew (yes or no) and, if yes, what they knew as an open-ended form.

The questionnaire was finalized through a pilot test using eight women to ensure that the questions are easy to understand and have a logical order. All data were collected via telephone interview conducted by trained interviewers. Each interviewer conducted three to four telephone interviews per day for up to 20 min each.

Data analysis

The data collected by telephone interviews were written down on the questionnaire sheet on the site, then simultaneously entered into EpiData (version 3.1) by two interviewers, and exported to Stata (version 16.1). Descriptive statistical analysis was performed to assess the frequencies of all variables.

Regarding the open-ended free responses on knowledge of cervical cancer (cause, symptoms, detection, and treatment), a panel of four gynecology specialists (two Cambodians and two Japanese) independently judged each answer, real expression by respondents, as "correct", "incorrect", or "unclassifiable", based on their clinical experiences and expertise. When three or more gynecologists judged "correct" or "incorrect", that answer was considered "correct" or "incorrect", respectively by the panel. Others were categorized as "unclassifiable".

A chi-square test was used to identify the association between characteristics and cervical cancer screening practices. Statistical significance was set at $p < 0.05$.

Ethical clearance

This study was ethically approved by the Cambodia National Ethics Committee for Health Research, Ministry of Health, Cambodia (No. 161 NECHR) and Institutional Review Board for Clinical Research, National Center for Global Health and Medicine, Japan

(NCGM-G-003434-00).

Informed consent was obtained from all participants before participation. The purpose of the study and assurance to withdraw at any step of the study without any disadvantages were fully explained and telephone interviews were conducted privately.

Results

Characteristics of study participants

Table 1 presents the characteristics of the study participants. A total of 100 women, 51 (51%) from four schools in urban districts and 49 (49%) from four schools in peri-urban districts, participated in this study. Their mean age was 47.9 ± 6.6 years, with 37 participants aged over 50 years. Of the 100 participants, 69 (69%) had graduated from high school or higher. The mean number of years of teaching experience was 26.7 ± 7.3 years. Most women had been married (88%) and had experience(s) of being pregnant (82%).

Knowledge of cervical cancer

All the study participants had heard of "cervical cancer", 94 (94%) had heard of "cervical cancer screening" and 91 (91%) had heard of "vaccination to prevent cervical cancer". When asked if they knew about the cause, symptoms, detection, and treatment of cervical cancer, "Don't know" was answered by 31 (31%) respondents for the causes, 44 (44%) for symptoms, 35 (35%) for detection, and 55 (55%) for treatment.

Among women who did not answer that they "Do not know", open-ended questions were asked regarding causes, symptom(s), detection, and treatment. One respondent could answer at least one or multiple answers to each open question. Each answer was labeled correct, incorrect, and unclassifiable, as shown in Supplemental Table S1 (*https://www.ghmopen.com/site/supplementaldata.html?ID=53*). Then, per study subject, some women replied "correct answer(s) only", or "at least one correct and other answer(s)" or "incorrect and/or unclassifiable answer(s) only". "Other answer(s) "here means either incorrect or unclassifiable answer(s).

As shown in Figure 1, of those who did not reply "Do not know", 1.5% (1/67), 68% (38/56), 97% (63/65), 62% (28/45) replied at least one correct answer regarding cause(s), symptom(s), detection, and treatment(s) respectively.

Consequently, among 100 study subjects, only 1, 38, 63, 28 respondents answered at least one correct answer(s) to cause(s), symptom(s), detection, and treatment.

Sources of information on cervical cancer

Figure 2 shows the sources of information on cervical cancer, screening, and vaccination to prevent cervical cancer. Although these items were asked separately, the sources of information were generally similar. The most common sources of information were relatives, friends, and colleagues, followed by doctors, television, and the Internet. Less than 10 answered radios, conferences, and newspapers. A small number of respondents reported that they actively obtained information from books, posters, and distributed leaflets.

Table 1. Characteristics of the study participants (*n* = 100)

Contents		*n* (%)	
Location of school	Urban district	51	(51%)
	Peri-urban district	49	(49%)
Age group	31-40	22	(22%)
	41-50	41	(41%)
	51-60	37	(37%)
Educational level	Secondary school	26	(26%)
	High school	43	(43%)
	College or higher	31	(31%)
Teaching experience	≤ 10	4	(4%)
	12-20	19	(19%)
	21-30	38	(38%)
	31-40	39	(39%)
Marital status	Married	79	(79%)
	Divorced/widowed	9	(9%)
	Not married	12	(12%)
Parity	Yes	82	(82%)
	No	18	(18%)

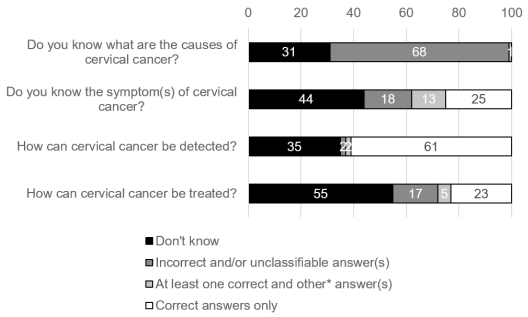

Figure 1. Knowledge of causes, symptoms, detection and treatment of cervical cancer.

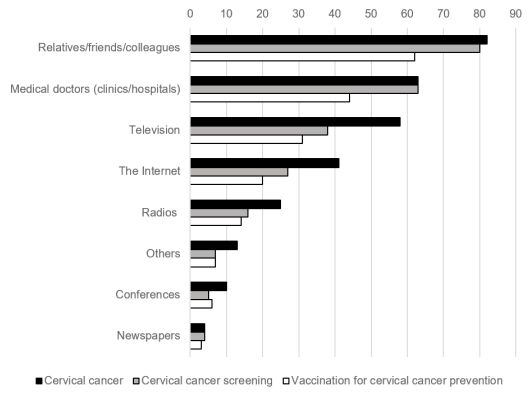

Figure 2. Sources of information about cervical cancer, screening, and vaccination (*n* = 100, multiple choice).

Table 2. Number and proportion of women who reported ever undergoing cervical cancer screening

Variables	Group	Total	Ever undergo cervical cancer screening		*p* value (χ^2 test)
		n	*n*	(%)	
Location of school	Urban	51	25	(50.0)	0.841
	Rural	49	24	(49.0)	
Age	31-40	22	13	(59.1)	0.361
	41-50	41	21	(51.2)	
	51-60	37	15	(40.5)	
Educational level	Secondary school	26	9	(34.6)	0.197
	High school	43	22	(51.2)	
	Collage and higher	31	18	(58.1)	
Marital status	No	12	0	(0)	< 0.001
	Yes	88	49	(55.7)	
Experience of health facility visit due to vaginal problem(s)	Yes	64	45	(70.3)	< 0.001
	No	36	4	(11.1)	
Provided at least one correct answer on cause	Yes	1	0	(0)	0.325
	No	99	49	(49.5)	
Provided at least one correct answer on symptom	Yes	38	20	(52.6)	0.570
	No	62	29	(46.8)	
Provided at least one correct answer on detection	Yes	63	34	(54.0)	0.195
	No	37	15	(40.5)	
Provided at least one correct answer on treatment	Yes	28	17	(60.7)	0.144
	No	72	32	(44.4)	

Experience of cervical cancer screening

Table 2 shows the number and proportion of study participants who underwent cervical cancer screening according to their sociodemographic characteristics. Among the 100 study participants, 49 (49%) had experience undergoing cervical cancer screening. Participants who were married and had experience in health facility visits due to vaginal problems were significantly more likely to have undergone cervical cancer screening ($p < 0.01$). Although not statistically significant, participants with higher educational levels were also more likely to have undergone cervical cancer screening. No particular tendency was observed between experience in cervical cancer screening and knowledge on cause, symptoms, detection, and treatment of cervical cancer.

Discussion

In this study, 100 female primary school teachers in Phnom Penh, Cambodia, were surveyed about their knowledge of cervical cancer, sources of information, and experiences of cervical cancer screening. A study in a rural province in Cambodia involving 440 women showed that 74 and 34% of women had heard about cervical cancer and screening (*10*). In another study on 443 female factory workers in Phnom Penh, 99% had heard of cervical cancer, but none of them knew about cervical cancer screening as a preventive measure (*18*). In contrast, in this study conducted among female primary school teachers in the Cambodian capital, over 90% of respondents had heard of both cervical cancer and screening. Open-ended questions were used for those who did not reply "Do not know" regarding cause(s), symptom(s), detection, and treatment(s) and revealed that many of their answers were judged as "incorrect" by gynecologists. As hesitation to answering "no" or "don't know", is often observed in surveys in Southeast Asia (*21*), our results also indicate so-called Courtesy bias and need to draw attention for a future similar study. All the study participants in this study had received secondary or higher education, and approximately 70% had received high school or higher education, far more than the average Cambodian woman (*22*). However, our results showed limited knowledge on the cause, symptoms, detection and treatment of cervical cancer, similar to previous reports of women in general and factory workers (*10,18*).

Experience of cervical cancer screening shows, unsurprisingly, those who are married and had experience in health facility visits due to vaginal problems were significantly more likely to have undergone screening. Although half of study participants had been screened previously, there was no significant relation between their cervical cancer screening experiences and knowledge of cervical cancer.

The sources of information were family and friends, followed by doctors, television, and the Internet. The main sources of information about cervical cancer were the same for women in general, female factory workers, and female elementary school teachers: family, relatives/friends, doctors, and the Internet (*10,18*). This suggests that these are the priority sources of information on cervical cancer in Cambodia, and it is important that correct information emanates from all of these sources. Since the second largest source of information was medical doctors, medical doctors and

health care professionals might have a role in providing correct knowledge of cervical cancer to the general population of women. It is important for doctors and medical personnel to be aware of their important role in cervical cancer health education including the provision of correct information on prevention as well as diagnosis and treatment.

In Asian countries including Cambodia, there is a strong hesitation to publically talk about sexual and reproductive health, and education regarding sexual and reproductive health can be difficult (*10,23-25*). This may relate to the fact that the most common source of information on cervical cancer was family and friends. To disseminate knowledge about cervical cancer to the general female population, it is necessary to consider effective methods that take into account the cultural background, such as broadcasting of culturally tailored video/sound (*26-28*) and culturally competent health education by local doctors and healthcare providers (*28*).

On the other hand, it also suggests that correct knowledge does not necessarily lead directly to correct behavior. One of the barriers is that the concept and practice of prevention are not widely recognized in society, and people do not consider it necessary to visit health facilities unless they have serious symptoms (*23,25,28*). Some people do not want to be identified as having cervical cancer by screening for fear that having cervical cancer will lead to social stigma and interfere with their daily lives due to discrimination and prejudice in the community (*23*). Moreover, lack of access to treatment has a direct association between cervical cancer and death or giving up and is a factor that keeps people away from seeking health care (*11,29,30*). Along with the implementation of culturally and socially appropriate health education, an improved understanding of cervical cancer throughout society without discrimination and stigma is also essential, which will result in improved access to health care that allows for cervical cancer screening and subsequent treatment. At the same time, an environment that enables early treatment of cervical cancer; medical facilities and equipment, quality health personnel, and establishment of a medical insurance system are needed.

The limitations of this study are that the sample size was small (100 study participants), and that the target population was a group of women living in the vicinity of the capital city and being educated at the secondary school level or above, which is not representative of the general female population in Cambodia. Although it is difficult to generalize simply, this study provides important basic information on the understanding of cervical cancer among primary school teachers in Phnom Penh.

Conclusion

Cambodia started its way toward the elimination of cervical cancer, in accordance with the global initiative (*5*). However, our study revealed that among female primary school teachers with above-average educational level in Cambodia, their knowledge of cervical cancer was generally low. It is important to improve the knowledge of primary school female teachers, who are potential key influencers of HPV vaccination to girls. To disseminate knowledge to promote cervical cancer prevention, it is necessary to provide correct knowledge in a broad and accessible manner through the involvement of local medical doctors and healthcare providers. Appropriate health education by health professionals may be an effective way to achieve this.

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ORIGINAL ARTICLE

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Association of atherogenic serum lipids and platelet activation with changes in arterial stiffness in patients with type 2 diabetes

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Abstract: Pulse wave velocity (PWV) is a potential marker for atherosclerosis severity and/or predictor of future atherosclerotic cardiovascular events. PWV is significantly correlated with carotid-intimal media thickness in patients with diabetes. However, its significance as a surrogate marker for the treatment of atherosclerotic cardiovascular risk in the management of type 2 diabetes has not been fully established. To elucidate the factors that determine the improvement or deterioration of PWV, we studied the association of clinical parameters, parameters for glucose metabolism, serum lipids including each lipoprotein fraction, serotonin as a marker for platelet activation, and change in PWV in 54 patients with type 2 diabetes. Systolic blood pressure and serum levels of non-high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol (LDL-C), and intermediate-density lipoprotein-cholesterol significantly decreased in the PWV-improved group after 2 months compared with those in the PWV-deteriorated group. The serotonin levels at baseline were significantly lower in the PWV-improved group than in the PWV-deteriorated group. The changes in systolic blood pressure and LDL-C levels were significantly and positively correlated with those in PWV. The serotonin levels at baseline were significantly and positively correlated with changes in PWV. Therefore, amelioration of blood pressure, serum lipid level, and platelet activation might be beneficially associated with PWV change. PWV-guided clinical practice for cardiovascular risk stratification could be useful in type 2 diabetes management.

***Keywords*:** atherosclerosis, diabetes, lipoprotein, pulse wave velocity, serotonin

Introduction

Type 2 diabetes and dyslipidemia are significant cardiovascular risk factors that should be managed (*1,2*). Therefore, it is important to regulate atherosclerotic risk factors and understand the progression of arteriosclerosis in patients with type 2 diabetes. Aortic pulse wave velocity (PWV) is an independent predictor of adverse cardiovascular events, including mortality (*3*). PWV reflects arterial stiffness and correlates with markers reflecting the severity of atherosclerosis, such as carotid intima-media thickness (IMT) (*4*). PWV is thought to be applicable as a marker for the severity of atherosclerosis and/or predictor of future atherosclerotic cardiovascular events (*4*). PWV has been significantly correlated with carotid IMT in patients with diabetes (*5,6*). Previous studies have reported that PWV can be beneficial in the clinical practice for cardiovascular risk stratification (*7,8*). However, its significance as a surrogate marker for the treatment of atherosclerotic cardiovascular risk in the management of type 2 diabetes has not been fully established.

Elevated of levels of atherogenic lipids, such as triglycerides (TG), low-density lipoprotein (LDL)-cholesterol (LDL-C), small dense LDL, and oxidized LDL as well as reduction of anti-atherogenic high-density lipoprotein (HDL)-cholesterol (HDL-C) level were observed in type 2 diabetes (*9*). Recently, attention has been focused on the important contribution of TG-rich lipoproteins, such as very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) to atherogenesis (*10*).

Serotonin is released from aggregating platelets and mediates platelet-induced vasoconstriction (*11*). In patients with diabetes, platelets are activated in endothelial injury promoted by atherosclerosis, and platelets are hyperreactive with intensified adhesion and aggregation (*12,13*). Activated platelets release serotonin stored in platelet-dense granules (*13*). It was previously reported that serotonin levels in platelet-poor plasma (PPP) increased in patients with coronary heart disease (CHD) (*14-16*). Platelet aggregatory response to serotonin is modulated by the disparate effects of lipoprotein fractions, corresponding to the recognized differences in the degree of atherogenicity of LDL and HDL (*11*). Amplification of serotonin-induced platelet

aggregation by LDL and its inhibition by HDL support the hypothesis that serotonin-mediated effects represent a mechanism clinically relevant to chronic progression of atherosclerosis (*11*).

To elucidate the factors that determine the improvement or deterioration of PWV, we studied the association of clinical parameters, parameters for glucose metabolism, serum lipids including each type of lipoprotein fraction, and serotonin level with the change in PWV.

Patients and Methods

A total of 54 patients with type 2 diabetes were recruited from the outpatient clinics in Kohnodai Hospital, National Center for Global Health and Medicine. We measured PWV, parameters for glucose metabolism, serum lipid profile, including each lipoprotein-cholesterol, and PPP serotonin at baseline and after 2 months. At 2 months, the treatments for diabetes, dyslipidemia, and hypertension were not changed intentionally. This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Medical Ethics Committee of the National Center for Global Health and Medicine (NCGM-G-000889). Written informed consent was obtained from each patient.

PWV was measured using a noninvasive vascular device with four pneumatic pressure cuffs (BP-203RPE, Omron Corp., Japan). Blood pressure levels and pulse waves were measured in the bilateral brachial and radial arteries after 5 min of rest on the bed. PWV was calculated as the transmission time and distance from the right or left arm to each ankle based on the body height. The mean value of the right and left PWV was used for analysis in this study.

Fasting plasma glucose, hemoglobin A1c (HbA1c), C-peptide, and small dense LDL levels were measured using commercial kits (HLC-723G and GA, Tosoh Corp., Japan; Sekisui Medical Co., Ltd., Japan; and Denka Seiken Co., Ltd., Japan, respectively).

The analysis method for lipoprotein profile using anion-exchange high-performance liquid chromatography (AEX-HPLC) has been previously reported (*17,18*). Briefly, major lipoprotein classes, HDL, LDL, IDL, and VLDL, in the plasma samples were separated using AEX-HPLC, and the cholesterol levels in the separated lipoprotein classes were measured using post-column reaction with a reagent containing cholesterol esterase and cholesterol oxidase. AEX-HPLC can be used as a substitute for ultracentrifugation. The PPP serotonin levels were measured using a previously reported method (*19*). In brief, PPP serotonin was separated in a column-switching system with two octadecyl-bonded silica columns. The separated serotonin was specifically converted into a fluorescent derivative with benzylamine and detected sensitively and quantitatively.

Data are presented as mean ± standard deviation. The Wilcoxon test was performed to compare the values at baseline and that after 2 months. The Mann-Whitney test and Fisher's exact probability test were performed to analyze the differences in data between the two groups. Correlations were estimated using the Spearman's rank test. Statistical significance was set at *P*-values of < 0.05.

Results

The clinical characteristics of patients with type 2 diabetes are summarized in Table 1. The mean body mass index and waist circumference were > 25 kg/m^2 and 0.9 m, respectively, suggesting that a relatively greater proportion of overweight and obese patients were included. Most patients were treated with insulin or oral anti-diabetic drugs. Approximately 60% and 70% of patients had used hypolipidemic and hypotensive drugs, respectively.

PWV and clinical and metabolic parameters at baseline and after 2 months of patients with type 2 diabetes are shown in Table 2. During the study period of 2 months, no intentional change in drugs was performed. No parameters, including PWV, showed significant changes. To determine the factors that improve or deteriorate PWV, we divided patients into PWV-improved (decreased) and PWV-deteriorated

Table 1.Clinical characteristics of studied patients with type 2 diabetes (*n* = 54)

Variables	Values
Age (years)	65.3 ± 11.1
Sex (male/female)	32/22
Smoker (smoker/non-smoker)	19/35
Duration for diabetes (years)	8.78 ± 9.72
Body mass index (kg/m^2)	25.6 ± 4.9
Waist circumference (m)	0.91 ± 0.12
Systolic blood pressure (mmHg)	141 ± 21
Diastolic blood pressure (mmHg)	80 ± 11
Pulse wave velocity (cm/sec)	1,774 ± 380
Anti-diabetic treatments (*n*)	
Insulin	10
Sulfonylurea	9
Glinides	5
Dipeptidyl peptidase-4 inhibitors	15
Thiazolidinedione	13
Metformin	31
a-glucosidase inhibitors	9
Hypolipidemic treatments (*n*)	
Statin	27
Fibrate	3
Ezetimibe	2
Anti-platelets treatments (*n*)	
Aspirin	5
Hypotensive treatments (*n*)	
Diuretics	1
Angiotensin converting enzyme inhibitors	2
Angiotensin II receptor blockers	19
b-blockers	2
Calcium antagonists	17

Table 2. Pulse wave velocity and metabolic parameters at baseline and after 2 months in patients with type 2 diabetes (*n* = 54)

Variables	Baseline	after 2 months	*P* value
Pulse wave velocity (cm/sec)	1,774 ± 380	1,777 ± 382	0.6421
Clinical parameters			
Body mass index (kg/m^2)	25.6 ± 4.9	25.5 ± 4.8	0.728
Waist circumference (m)	0.91 ± 0.12	0.91 ± 0.11	0.797
Systolic blood pressure (mmHg)	141 ± 21	139 ± 19	0.420
Diastolic blood pressure (mmHg)	80 ± 11	79 ± 10	0.115
Parameters for glucose metabolism			
Fasting plasma glucose (mg/dL)	135 ± 28	134 ± 26	0.436
Hemoglobin A1c (%)	7.2 ± 0.9	7.2 ± 0.8	0.781
Fasting serum C-peptide (ng/mL)	1.73 ± 0.7	1.92 ± 1.0	0.280
Serum lipids			
Triglyceride (mg/dL)	114 ± 47	112 ± 50	0.390
Non-HDL-C (mg/dL)	128 ± 26	123 ± 26	0.091
LDL-C (mg/dL)	116.3 ± 26.0	113 ± 25.3	0.240
IDL-C (mg/dL)	6.6 ± 2.1	6.7 ± 2.6	0.607
VLDL-C (mg/dL)	12.1 ± 7.3	11.1 ± 7.0	0.155
HDL-C (mg/dL)	58.3 ± 16.0	58.1 ± 15.3	0.904
Small-dense LDL (mg/dL)	27 ± 11	27 ± 12	0.801
Oxidized LDL (U/mL)	92 ± 28	95 ± 24	0.740
Serotonin levels			
PPP serotonin (nmol/L)	20.9 ± 19.6	22.7 ± 17.2	0.196

Abbreviations: Non-HDL-C, non-high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; IDL-C, intermediate-density lipoprotein-cholesterol; VLDL-C, very-low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; PPP, platelet-poor plasma.

Table 3. Differences in clinical characteristics, parameters for glucose metabolism, serum lipids and serotonin between PWV-improved group and PWV-deteriorated group

Variables	PWV-improved group (*n* = 25)			PWV-deteriorated group (*n* = 28)			Comparison between 2 groups	
	Baseline	after 2 months	*P* values *vs*. baseline	Baseline	after 2 months	*P* values *vs*. baseline	*P* values at baseline	*P* values after 2 months
Clinical parameters								
Body mass index (kg/m^2)	26.1 ± 5.4	26.1 ± 5.1	0.379	25.2 ± 4.5	24.9 ± 4.5	0.223	0.521	0.368
Waist circumference (m)	0.92 ± 0.13	0.92 ± 0.13	0.346	0.91 ± 0.1	0.90 ± 0.1	0.288	0.726	0.368
Systolic blood pressure (mmHg)	140 ± 21	135 ± 17	0.044	141 ± 21	143 ± 20	0.235	0.470	0.076
Diastolic blood pressure (mmHg)	79 ± 10	77 ± 8	0.053	81 ± 12	80 ± 11	0.392	0.762	0.184
Treatments								
Calcium antagonists (*n*)	12	12	NA	5	5	NA	0.020	0.020
Parameters for glucose metabolism								
Fasting blood glucose (mg/dL)	127 ± 23	133 ± 23	0.029	141 ± 30	135 ± 29	0.197	0.149	0.817
Hemoglobin A1c (%)	7.1 ± 0.8	7.1 ± 0.7	0.354	7.3 ± 1.0	7.2 ± 0.8	0.489	0.438	0.464
Fasting serum C-peptide (ng/mL)	1.9 ± 0.8	2.1 ± 1.2	0.173	1.6 ± 0.6	1.7 ± 0.9	0.308	0.250	0.107
Serum lipids								
Triglyceride (mg/dL)	112 ± 34	115 ± 56	0.495	116 ± 56	108 ± 47	0.127	0.728	0.669
Non-HDL-C (mg/dL)	140 ± 26	129 ± 28	0.014	117 ± 21	118 ± 22	0.400	0.001	0.086
LDL-C (mg/dL)	128.6 ± 26.6	118.2 ± 28.0	0.016	104.9 ± 20.5	107.4 ± 22.5	0.233	0.001	0.139
IDL-C (mg/dL)	6.6 ± 1.4	6.1 ± 1.7	0.010	6.6 ± 2.5	6.9 ± 2.9	0.239	0.510	0.392
VLDL-C (mg/dL)	11.1 ± 4.3	11.3 ± 7.3	0.404	12.8 ± 9.3	10.8 ± 7.0	0.055	0.880	0.715
HDL-C (mg/dL)	58.8 ± 14.9	55.8 ± 13.7	0.069	58.8 ± 17.4	60.3 ± 16.7	0.052	0.748	0.285
Small-dense LDL (mg/dL)	31.5 ± 10.7	30.6 ± 13.0	0.295	23.1 ± 9.1	25.0 ± 10.3	0.135	0.001	0.024
Oxidized LDL (U/mL)	97 ± 27	99 ± 24	0.371	88 ± 28	91 ± 18	0.193	0.240	0.247
Serotonin levels								
PPP serotonin (nmol/L)	14.7 ± 9.3	19.0 ± 10.5	0.038	26.2 ± 24.3	23.6 ± 19.2	0.477	0.032	0.466

Abbreviations: Non-HDL-C, non-high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; IDL-C, intermediate-density lipoprotein-cholesterol; VLDL-C, very-low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; PPP, platelet-poor plasma; NA, not applicable.

(increased) groups and analyzed the differences between both groups. Table 3 shows the differences in clinical parameters, parameters for glucose metabolism, serum lipid levels, and PPP serotonin levels between the PWV-improved and PWV-deteriorated groups.

Systolic blood pressure significantly decreased in the

PWV-improved group after 2 months. A significantly greater number of patients had used calcium antagonists at baseline and after 2 months in the PWV-improved group than in the PWV-deteriorated group. Fasting blood glucose levels significantly increased in the PWV-improved group. Serum levels of non-high-density lipoprotein-cholesterol (non-HDL-C), LDL-C, and IDL-cholesterol (IDL-C) significantly decreased after 2 months in the PWV-improved group. Serum non-HDL-C, LDL-C, and small-dense LDL levels at baseline and small-dense LDL levels after 2 months were significantly higher in the PWV-improved group than in the PWV-deteriorated group. PPP serotonin levels significantly increased in the PWV-improved group. However, PPP serotonin levels at baseline were significantly lower in the PWV-improved group than in the PWV-deteriorated group.

We analyzed the correlation of parameters that showed a significant change with change in PWV. The correlation of changes in systolic blood pressure and fasting blood glucose, non-HDL-C, LDL-C, IDL-C, and PPP serotonin levels with changes in PWV is shown in Figure 1. Changes in the systolic blood pressure and LDL-C levels were significantly and positively correlated with changes in PWV. However, changes in the fasting blood glucose, non-HDL-C, IDL-C, and PPP serotonin levels were not significantly correlated with changes in PWV.

The parameters for clinical characteristics, glucose metabolism, and serum lipids were not significantly correlated with PPP serotonin levels at baseline or after 2 months. Furthermore, changes in any parameters did not correlate with that in PPP serotonin levels. The correlations of PPP serotonin levels with PWV at baseline or after 2 months and with the change in PWV are shown in Figure 2. PPP serotonin levels at baseline were significantly and positively correlated with changes in PWV.

Discussion

Since 2001, PWV measurement has been applied for the risk stratification of patients with atherosclerotic cardiovascular disease and/or its risk factors in Japan (*4*). Several cross-sectional studies have demonstrated a significant correlation between PWV and known risk factors for cardiovascular diseases. The treatment of cardiovascular risk factors and lifestyle modifications have been shown to improve PWV (*4*).

Several meta-analyses have demonstrated that PWV reduces by antihypertensive treatments (*20-23*). A significant reduction in systolic blood pressure in the PWV-improved group and a significant and positive correlation between changes in systolic blood pressure and PWV suggest that a reduction in systolic blood pressure is beneficially associated with PWV.

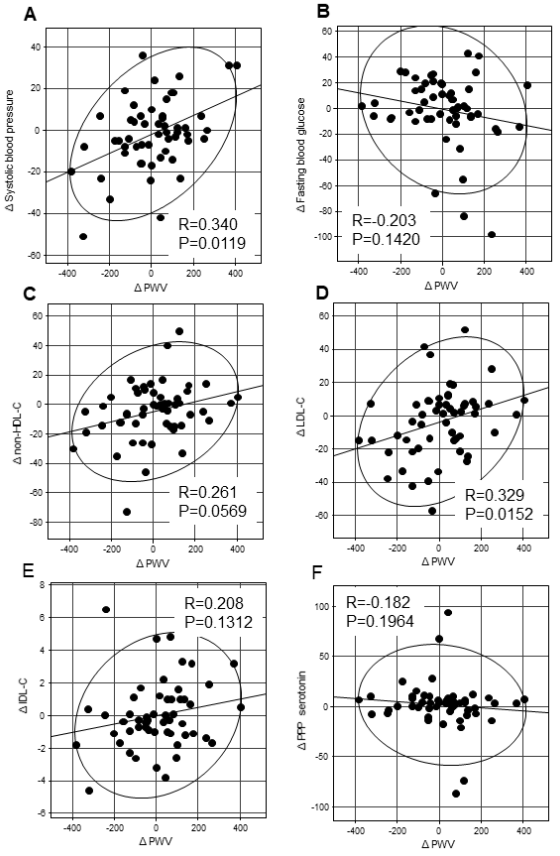

Figure 1. Correlation of changes in the systolic blood pressure (A) and fasting blood glucose (B), non-high-density lipoprotein-cholesterol (non-HDL-C) (C), low-density lipoprotein-cholesterol (LDL-C) (D), intermediate-density lipoprotein-cholesterol (IDL-C) (E), and platelet-poor plasma (PPP) serotonin (F) levels with the change in pulse wave velocity (PWV). R indicates the correlation coefficient.

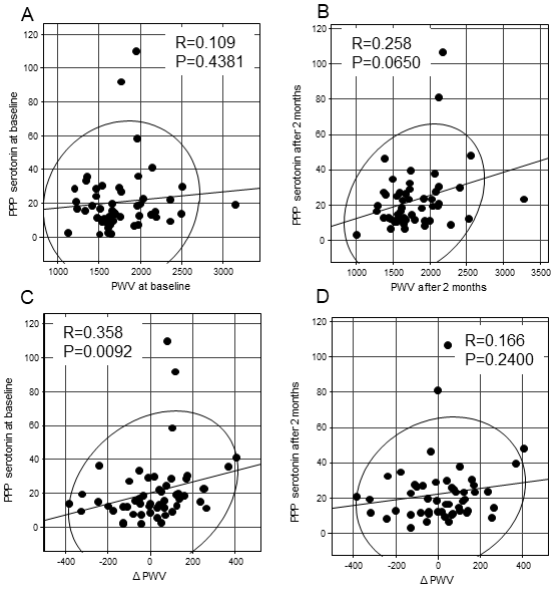

Figure 2. Correlations of the platelet-poor plasma (PPP) serotonin levels with pulse wave velocity (PWV) at baseline (A) and after 2 months (B) and with the change in PWV at baseline (C) and after 2 months (D). R indicates the correlation coefficient.

In a previous study with 4938 healthy adults, the sample was categorized into four groups using the 75 g oral glucose tolerance test (*24*). PWV increased in the following order: normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance, and newly diagnosed diabetes (*24*). Another study showed that PWV increased in the order of normal subjects, patients with impaired fasting glucose, and patients with diabetes and was positively correlated with fasting blood glucose and HbA1c levels (*25*). Although fasting blood glucose levels significantly increased in the PWV-improved group, fasting blood glucose levels at baseline or after 2 months in the PWV-improved group were lower than those in the PWV-deteriorated group. Furthermore, no significant correlation between changes in fasting blood glucose levels and PWV was observed. In our patients, fasting blood glucose levels may not be associated with the determination of PWV.

Atherogenic dyslipidemia comprises a triad of increased blood small dense LDL, decreased HDL, and TG levels (*26*). As a typical feature of type 2 diabetes, atherogenic dyslipidemia has emerged as an important coronary risk factor. The Framingham Heart Study (2,693 men, 3,101 women) has shown that non-HDL-C level is a stronger predictor of CHD risk than LDL-C (*27*). An abundance of small dense LDL increases CHD risk by three-fold (*28*). The metabolic milieu associated with small dense LDL includes insulin resistance, increased IDL, increased susceptibility to oxidative damage, impaired reverse cholesterol transport, and increased postprandial lipemia (*28*). A significant decrease in non-HDL-C, LDL-C, and IDL-C levels was observed in the PWV-improved group compared with in the PWV-deteriorated group. This decrease might be beneficially associated with PWV. In our study, low-density LDL levels in the PWV-improved group at baseline or after 2 months were significantly higher than those in the PWV-deteriorated group. However, small dense LDL decreased in the PWV-improved group and increased in the PWV-deteriorated group, thereby diminishing the negative impact of high small dense LDL levels on PWV in the PWV-improved group. Otherwise, a significant reduction in non-HDL-C, LDL-C, and IDL-C levels might have diminished the negative impact of high small dense LDL levels on PWV in the PWV-improved group.

Accelerated atherosclerosis and increased risk of thrombotic vascular events in patients with diabetes may result from dyslipidemia, endothelial dysfunction, platelet hyperreactivity, impaired fibrinolytic balance, and abnormal blood flow. The importance of platelets in the atherothrombotic process has led to the investigation for the use of antiplatelet agents to reduce cardiovascular risks. A meta-analysis conducted by the Antiplatelet Trialists' Collaboration demonstrated that aspirin reduced the risk of ischemic vascular events as a secondary prevention strategy in numerous high-risk groups, including patients with diabetes (*29*). Activated platelets release serotonin stored in platelet-dense granules (*13*). In the present study, significantly lower PPP serotonin levels were observed in the PWV-improved group than in the PWV-deteriorated group, suggesting a significant contribution of serotonin to atherogenesis. Furthermore, the PPP serotonin levels at baseline were significantly and positively correlated with changes in PWV. The PPP serotonin levels have been reported to be increased in patients with CHD (*14-16*), supporting our results.

Our study showed that a significantly greater number of patients had used calcium antagonists at baseline and after 2 months in the PWV-improved group compared with that in the PWV-deteriorated group. Calcium antagonists have been reported to inhibit the amplifying effect of LDL on serotonin-induced platelet aggregation (*11*). In our study, the PPP serotonin levels in patients receiving calcium antagonists (n = 16, 15.7 ± 13.2 nmol/L) were lower than those in patients who were not receiving calcium antagonists (n = 36, 23.2 ± 21.6 nmol/L) (P = 0.057). Furthermore, PWV decreased in patients using calcium antagonists (n = 17, −57 ± 176 cm/s) but increased in patients who had not used calcium antagonists (n = 37, 37 ± 149 cm/s) (P = 0.053). This suggested a possible beneficial effect of calcium antagonists on PWV. A meta-analysis showed that calcium antagonists significantly reduced PWV compared with placebo in long-term trials (*20*). However, calcium antagonists did not show superiority in improving PWV compared with other types of antihypertensive drugs. Further studies are needed to elucidate the influence of antihypertensive drugs on PWV.

The Steno-2 study demonstrated that intensified multifactorial intervention with tight glucose regulation and the use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents had sustained beneficial effects with respect to vascular complications and on mortality rates from any cause, including cardiovascular causes (*30*). While no parameters improved in the PWV-deteriorated group, four parameters were significantly improved in the PWV-improved group, suggesting that the improvement of multiple coronary risk factors led to an improvement in PWV.

This study has some limitations. First, the number of participants was small. Second, since this was an observational study, the causal relationship of the results could not be explained clearly. To elucidate the influence of metabolic parameters on PWV, a randomized controlled trial using interventions is recommended in the future.

In conclusion, a reduction in blood pressure; a decrease in the levels of atherogenic lipids, including non-HDL-C, LDL-C, and IDL-C; and lower levels of platelet activation might be beneficially associated with PWV. PWV-guided clinical practice for cardiovascular

risk stratification could be useful in the management of type 2 diabetes.

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BRIEF REPORT

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Safety of convalescent plasma therapy for COVID-19 patients and analysis of viral kinetics: A single-center, open-label, single-arm, interventional study in Japan

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Abstract: Convalescent plasma therapy is an important treatment method for patients with severe coronavirus disease (COVID-19). This study was conducted to confirm the safety of this therapy. We conducted an open-label clinical trial to administer convalescent plasma transfusion in a small Japanese cohort. Blood was collected from the recovered COVID-19 patients with high anti-severe acute respiratory syndrome coronavirus 2 (anti-SARS-CoV-2) spike IgG titer and high neutralizing activity and stored in the National Center for Global Health and Medicine Hospital until use. Convalescent plasma was administered to COVID-19 patients who required supplemental oxygen within 3 days of hospitalization. Convalescent plasma was administered to 11 patients with moderate to severe COVID-19. One patient experienced an adverse event, such as redness of the skin around the intravenous injection site within 3 hours after transfusion. Ten patients (91%) showed clinical improvement within 28 days, and one patient died of causes unrelated to plasma therapy. The data suggest that patients with COVID-19 examined in the present study received convalescent plasma without having any significant adverse effects. We plan to conduct a randomized controlled trial to examine the clinical effectiveness of convalescent plasma transfusion in a large Japanese COVID-19 cohort.

***Keywords*:** SARS-CoV-2, hospitalization, safety study, adverse event, Japan

Introduction

The coronavirus disease (COVID-19) epidemic began in December 2019, and as of November 2021, more than 250 million infections and 5 million deaths have been reported (*1*). Although some standard treatments such as remdesivir and dexamethasone have been established (*2*), resistance to remdesivir has been reported (*3*), and therapeutic agents with antiviral activity, in particular, continue to be in demand.

Convalescent plasma therapy was classically used to treat patients with the Spanish flu and has been reported to be effective (*4*). More than 40 years ago, a randomized controlled trial conducted on cases of Argentine hemorrhagic fever (*5*), one of the South American hemorrhagic fevers, revealed that the therapy reduced the fatality rate. In recent years, convalescent plasma therapy has been used for severe infections such as H5N1 avian influenza and Ebola hemorrhagic fever (*6,7*), as well as severe acute respiratory syndrome and Middle East respiratory syndrome (*8-10*), which are infections caused by the same coronavirus as the new coronavirus.

Several clinical studies of convalescent plasma therapy for COVID-19 have been reported in China (*11*), India (*12*), the United States (*13*), and South America (*14*), but it has never been implemented in Japan. This is the first report on convalescent plasma therapy in Japan,

and we conducted a safety evaluation and virological analysis.

Materials and Methods

This study was designed as an open-label, single-arm, interventional study with only the convalescent plasma group and was conducted at the National Center for Global Health and Medicine (NCGM) in Tokyo, Japan.

Recruitment of COVID-19 convalescent patients was performed for plasma collection (*15*). Blood samples were taken from COVID-19 recovering patients who were at least 3 weeks from the date of onset for measurement of laboratory data. Hemoglobin, spike protein antibodies, and neutralizing activity were examined at the National Center for Global Health and Medicine Research Institute. Screening for infectious diseases (hepatitis B virus (HBV) surface antigen (Ag), HBV core antibody (Ab), HBV surface Ab, hepatitis C virus (HCV) Ab, human immunodeficiency virus (HIV)-1 Ab, HIV-2 Ab, HBV DNA, HCV RNA, hepatitis E virus RNA, HIV-1 RNA, HIV-2 RNA, *Treponema pallidum* Ab, human T-cell lymphoma virus 1 Ab, human T-cell lymphoma virus 2 Ab, and human parvovirus B19 Ag), blood type tests, and irregular antibody testing were performed at the Japanese Red Cross Central Blood Institute, while severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR tests in plasma were performed at the National Institute of Infectious Diseases, Department of Safety Research on Blood and Biological Products (*16*). Spike protein was measured based on the methods previously reported (*17,18*), and patients whose plasma sample, absorbance value at optical density (OD) 450 nm was > 1, were considered to be eligible as donors. As a neutralizing activity, the concentration of IgG required for 50% inhibition of viral infection (IC_{50}) was evaluated according to the methods reported previously (*19*). Plasma with less than 50 μg/mL of IC_{50} was considered eligible. Cases with positive infectious disease screening tests or irregular antibodies were excluded, as were cases with positive polymerase chain reaction (PCR) tests for SARS-CoV-2 in serum. Four hundred mL of plasma was collected from eligible convalescent patients using a blood cell separator, and the plasma was stored below -20°C in a freezer at the National Center for Global Health and Medicine Research Institute. Plasma to be administered to the patient was obtained from plasma that was compatible with the patient's and donor's blood types, starting with the oldest date of collection.

The patients to whom plasma was administered were diagnosed with COVID 19 by PCR or antigen testing, and required supplemental oxygen. Patients aged under 20 years, pregnant or lactating women, those whose religious beliefs do not allow for the administration of blood transfusions, those participating in other treatment studies for COVID-19, and those whose physicians deemed inappropriate for inclusion in the study were excluded. Eligible patients were given 200 mL plasma within 3 days of admission after providing written consent. The plasma to be administered was matched to the blood type of the recipient patient. Plasma was thawed spontaneously, cross-matching was performed, and plasma was administered after confirming the cross-matching results. Convalescent plasma was administered *via* a peripheral vein starting at 10 mL/15 min and then increasing the flow to 100 mL/h.

Initially, the primary endpoint was set as the absence of ventilatory management or death by day 14 of treatment, but this was judged to be difficult to evaluate because of the small number of participants in this study due to the planned start of a randomized controlled trial, so the aim was changed to an evaluation of the safety of convalescent plasma therapy. The primary endpoint was the presence or absence of adverse events within 28 days of plasma administration. An adverse event was defined as any unwanted or unintended symptom (including abnormal laboratory test results), condition, or illness that occurred within 28 days after convalescent plasma administration. The presence of adverse events was assessed daily during hospitalization and on days 3, 7, 14, and 28 after plasma administration, which was the day of the outpatient visit after discharge. Secondary endpoints included changes in SARS-CoV-2 viral load in nasopharyngeal swabs (pre-dose to day 14) and clinical improvement was monitored up to 28 days using an 8-point scale and the National Early Warning Score. Nasal swabs were collected before and 3, 7, 14, and 28 days after plasma administration. The SARS-CoV-2 viral copy number in each sample was determined as previously described and the threshold cycle (Ct) values were obtained (*20*). To calculate the copy numbers of SARS-CoV-2 from the Ct values, a standard curve was generated with 10-fold serial dilutions of a reference SARS-CoV-2 viral RNA (*19*), and the Ct values for each sample were converted to SARS-CoV-2 copy numbers. The 8-point scale was: 1. Dead; 2. Hospitalized and using invasive mechanical ventilation or extracorporeal membrane oxygenation; 3. Hospitalized and using noninvasive ventilation or high-flow oxygenation; 4. Hospitalized and needing oxygen supplementation; 5. Hospitalized and needing no oxygen supplementation – requiring continuation of treatment (COVID-19-related or other); 6. Hospitalized and needing no oxygen supplementation – needing no continuation of treatment; 7. Not hospitalized and needing limitation of activities and/or oxygen therapy at home; 8. Not hospitalized, and no limitation of activities.

This study was approved as a specified clinical trial in October 2020 in the NCGM and registered in the Japanese Register of Clinical Trials (jRCTs031200124).

Table 1. The characteristics, COVID-19 treatment, plasma side effects and outcome of 11 COVID-19 patients who received a convalescent plasma transfusion

	Age (years)	Sex	Underlying diseases	Treatment for COVID-19	Days from COVID-19 onset to plasma administration	Oxygen dose at the time of plasma administration	Oxygen dose at the worst point of respiratory condition	Intubation or death	Adverse event	Outcome
1	46	M	HIV infection	REM/DEX	10	1 L/min	4 L/min	None	None	Recovery
2	59	M	Diabetes, hypertension, COPD, hyperlipidemia	REM/DEX	8	NHF	NHF	None	None	Recovery
3	46	M	Hypertension, obesity	REM/DEX	7	1 L/min	2 L/min	None	None	Recovery
4	39	M	None (Previous history of hepatitis B)	DEX	12	2 L/min	5 L/min	None	None	Recovery
5	61	M	Membranous nephropathy, bronchial asthma, hyperuricemia, dyslipidemia	REM/DEX	12	4 L/m	5 L/min	None	None	Recovery
6	61	M	Interstitial pneumonia	REM/DEX	7	2 L/m	2 L/min	None	None	Recovery
7	60	M	Hypertension	REM/DEX	8	2 L/m	2 L/min	None	None	Recovery
8	64	F	Osteoporosis	REM/DEX	10	4 L/min	NHF	None	Erythema at the infusion site	Recovery
9	90	F	Interstitial pneumonia, hypertrophic heart disease, hypertension	REM/DEX	9	5 L/min	NHF	Yes	None	Death
10	66	M	Hypertension	REM/DEX	7	3 L/min	NHF	None	None	Recovery
11	86	F	Hypertension, dyslipidemia	REM/DEX	6	1 L/min	1 L/min	None	None	Recovery

COVID-19, coronavirus disease; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; REM, remdesivir; DEX, dexamethasone; F, female; M, male; NHF, nasal high-flow therapy.

Results and Discussion

From October 1, 2020, to December 31, 2020, 11 patients were enrolled in the study (Table 1). Eight (72.7%) patients were men, and the median age was 61 years. All patients had underlying medical conditions. The median day from onset to plasma administration was 8 days. All patients received dexamethasone during the study, and all but one received remdesivir. All patients were on oxygen at the time of enrollment. One patient died and the other ten were discharged. The data and safety monitoring committee determined that the patient's death was not causally related to the plasma administration. One patient developed erythema at the puncture site the plasma transfusion. Of the 11 COVID-19 patients who received convalescent plasma, five underwent infectious disease screening tests 90 days after administration, and all were negative.

Figure 1 shows the relationship between the number of days elapsed from the date of administration of the convalescent plasma and the percentage of recovered COVID-19 patients, defined as the criteria for category 6, 7, or 8 on the 8-point scale. Four patients (36%) recovered within 7 days of treatment, 7 (64%) within 14 days, and 10 (91%) within 28 days.

Figure 2 shows the trend of SARS-CoV-2 viral load in nasal swabs as a function of the number of days elapsed from the onset date. Counting from the date of onset, none of the patients had the virus undetectable within 10 days of onset, three patients (27%) had the virus below the detection limit within 20 days, 7 (64%) patients within 30 days, and 9 (82%) patients within 40 days, and two patients (18%) did not disappear until 30 or 34 days after onset. Starting from the administration of plasma, two patients (18%) disappeared within 7 days after plasma administration, 7 (64%) within 14 days, 9

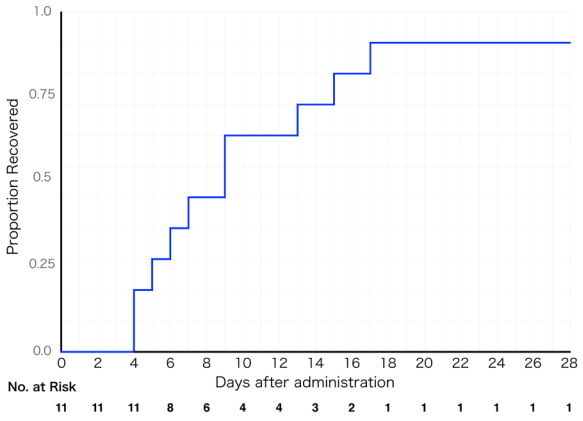

Figure 1. The relationship between the number of days elapsed from the date of administration of the convalescent plasma and the percentage of COVID-19 patients discharged from the hospital. No, number; COVID-19, coronavirus disease.

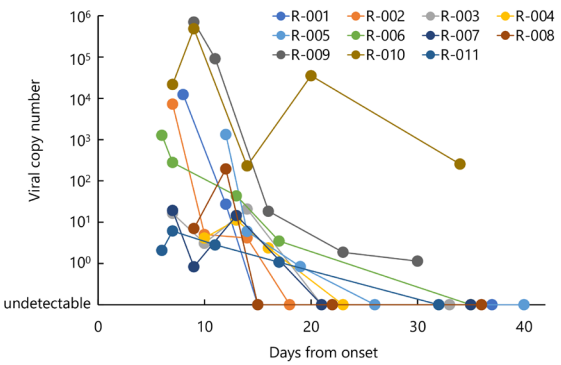

Figure 2. The trend of SARS-CoV-2 viral load in nasal swabs as a function of the number of days elapsed from the onset date. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

(82%) within 28 days, and two patients (18%) still had detectable virus 28 days after administration.

Eleven COVID-19 patients received convalescent plasma, and no adverse events related to plasma administration were identified, except for redness at the site of intravenous injection after administration. Although convalescent plasma therapy for COVID-19 has been used overseas, this is the first time that this therapy has been implemented in Japan. The establishment of a system for the safe administration of convalescent plasma in Japan is considered significant.

Although the number of COVID-19 patients to whom we have administered convalescent plasma is small (11 patients), a larger number of patients have been administered COVID-19 overseas, and the safety of COVID-19 has been verified. In the United States, 22,000 COVID-19 patients have been treated with convalescent plasma and analyzed for adverse effects (*21*). In this analysis, complications included the following: transfusion reactions in 89 (< 1%), thromboembolic complications in 87 (< 1%), cardiac events in 680 (approximately 3%), and the majority of thromboembolic and cardiac events were judged to be unrelated to the plasma. These results show that the incidence of transfusion reactions with convalescent plasma appears to be comparable with that of standard plasma when applied to a patient population with similar illness severity.

In our study, 10 of 11 patients recovered, and one died (mortality rate 9.1%). According to data from COVID-19 Registry Japan (COVIREGI-JP) (*22*), a Japanese registry of COVID-19 hospitalized patients, the mortality rate for patients requiring oxygen or ventilatory management on admission is 17.7%. It is difficult to simply compare the results of this study with those of COVIREGI-JP because of the two studies used different definitions of disease severity. Randomized controlled trials (RCTs) to determine the efficacy of convalescent plasma therapy have been conducted in other countries, and the results of some RCTs have been reported to date. Multiple RCTs have shown that the administration of convalescent plasma to hospitalized patients who require oxygenation or who are severely ill with COVID-19 is not expected to be effective (*11,12,23*). This may be because in patients with advanced disease, viral replication has ceased and the focus of the disease is on an excessive inflammatory response, so the time when convalescent plasma, whose mechanism of action is to neutralize the virus, is no longer effective.

In contrast, an RCT in which convalescent plasma was administered within 3 days of disease onset to older patients and patients at high risk of severe disease with underlying disease showed that it prevented severe disease (*14*). Furthermore, Sullivan *et al.* reported that early administration of high-titer SARS-CoV-2 convalescent plasma reduced outpatient hospitalizations by more than 50% (*24*). However, in another RCT, convalescent plasma was administered within 7 days of onset, but no efficacy was demonstrated (*25*). These results suggest that convalescent plasma is unlikely to be effective in already severe disease, and that administration of plasma with high antibody titers as soon as possible after the onset of disease is most likely to be effective. In addition, in the RCTs conducted to date, the neutralizing activity of the collected plasma was not assessed prior to administration, but only the IgG titer was assessed. In fact, it has been reported that plasmas or purified-IgG with high-neutralizing activity significantly reduced the viral induced lung lesions in SARS-CoV-2 infected Syrian hamsters (*26*).

We have reported that IgG titer and neutralizing activity can sometimes deviate in convalescent patients, and neutralizing activity may not be accurately assessed by measuring IgG titers alone (*19*). In this study, we assessed the neutralizing activity in the collected plasma, in order to assess the plasma quality more accurately. In the future, the efficacy of convalescent plasma therapy could be validated by conducting a randomized controlled trial in high-risk patients with early onset of disease, using plasma that has been previously evaluated for neutralizing activity to be administered. The antibodies possessed by the convalescent patients are a wide variety of polyclonal ones, only a few of which have neutralizing activity against the virus. A homogeneous monoclonal antibody preparation with high neutralizing activity has been shown to be effective in patients with early-onset COVID-19 (*27,28*). Now that monoclonal antibody products are available, the role of convalescent plasma therapy is limited, but it remains a potential treatment option in developing countries and could be a treatment option for the next emerging infectious disease.

In this study, we also observed changes in the viral load of SARS-CoV-2 in the nasal swabs of 11 patients. In a study analyzing the viral load of SARS-CoV-2 in 655 COVID-19 patients (40% of whom required oxygen administration), the median time for the virus

to fall below the limit of detection in patients older than 65 years was 16 days after onset, and 12 days in those younger than 65 years (*29*). In our study, the median time for viral load to fall below the detection limit in nine patients was 21 days, and two patients virus was still detectable 28 days after transfusion. With these results, it is not possible to show the effect of the administration of convalescent plasma on the reduction of viral load. The fact that the 11 patients in our study had a higher severity of illness than the COVID-19 patients in the study by Néant *et al.* may be related to the longer viral disappearance time. In addition, since this study did not examine the efficacy of convalescent plasma, but rather focused on evaluating safety, it is not possible to determine the efficacy of convalescent plasma because of the disparate neutralizing activities of the plasma administered.

In conclusion, this is the first study of plasma therapy for COVID-19 patients to be conducted in Japan. No treatment-related adverse events were observed in the 11 patients who received plasma therapy. A randomized controlled trial using plasma with pre-evaluated neutralizing activity is needed to determine the efficacy of plasma therapy in patients with moderately severe COVID-19.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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BRIEF REPORT

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Global landscape of the COVID-19 vaccination policy: Ensuring equitable access to quality-assured vaccines

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Abstract: Ensuring equitable access to COVID-19 vaccines for all people has been challenging, hence, establishing relevant vaccination policies is required. This study delineates how vaccination policies have affected equitable access to COVID-19 vaccines. A situation survey was conducted in 201 countries and territories through 156 Japanese diplomatic missions abroad to capture the global state of COVID-19 vaccination policies. Questionnaire responses were received from 159 states (79%) as of March 31, 2021, and data from Japan were incorporated into the analysis. All questionnaire items were open-ended, covering the vaccines in use and five vaccination policies such as vaccine eligibility. Results reveal that first, 81 states (51% out of 160) had not started vaccinations as of February 24, 2021, but by March 31, this number had decreased dramatically to 37 (23%); in particular, the number of states in Africa without vaccination decreased from 40 to 16. Second, 43 (27%) states did not recommend the vaccine for pregnant women. Third, the vaccine was free of charge to the public in 116 states (73%), and 43 states (27%) offered no-fault compensation. Finally, vaccination was voluntary in 124 states (78%). In conclusion, the number of countries that had started vaccination increased by March 2021, especially in Africa, although many African countries seemed to lack access to the mRNA vaccine. To fix the uneven distribution, dose donations were accelerated since middle of July. Reviewing worldwide vaccine policies is useful not only for this pandemic but also to strengthen vaccination systems for preparedness for the next pandemic.

***Keywords*:** vaccine policy, equity, COVAX Facility, mRNA, no-fault compensation, voluntary inoculation

Introduction

The year 2020 brought a global pandemic caused by the new coronavirus infection; on January 30, the World Health Organization (WHO) Director-General declared the virus a Public Health Emergency of International Concern (PHEIC) (*1*). In response to what was later declared a pandemic, vaccine development began worldwide, and pre-purchase negotiations for COVID-19 vaccine candidates heated up among developed countries from the early stages. To ensure equitable access to the COVID-19 vaccine for all regardless of national economic power, Gavi, the Vaccine Alliance (Gavi), Coalition for Epidemic Preparedness Innovations (CEPI), and WHO established a global mechanism known as "COVID-19 Vaccine Global Access Facility (COVAX Facility)" for pooled procurement and distribution of vaccines (*2*). The COVAX Facility aimed to ensure equitable access to vaccines with guaranteed safety, efficacy, and quality for all nations, including developing countries. With this study, we aimed to assess the state of vaccine delivery worldwide and vaccine policy in each country as of March 31, 2021, using survey data; we selected the end of March because the COVAX Facility had begun delivering vaccines approximately one month earlier. Our aim was to understand the direction of vaccine policies and how to expand equitable access to vaccines both as an effective countermeasure against COVID-19 and to prepare for future global pandemics.

Methods

Generating the data

To determine the status of the global COVID-19 vaccination policy, the Ministry of Foreign Affairs in

Japan sent a survey request to the Japanese diplomatic missions abroad, which covered 201 countries and territories. As of March 31, 2021, the questionnaires were returned by 159 (79%) states. Besides incorporating these responses, we also include the status of the vaccination policy in Japan as of March 31, 2021. All survey items were open-ended questions on topics that had been developed by the International Affairs Division, Minister's Secretariat of Ministry of Health, Labour and Welfare and the Global Health Policy Division, International Cooperation Bureau, Ministry of Foreign Affairs. For this study, we selected several responses to questions that could be categorized into quantitative data from qualitative responses, such as which vaccine the country used and the start date of vaccination.

Measures

The vaccines: The vaccines were identified using the developers' names taken from the COVID-19 candidate vaccine landscape and tracker (*3*). Items and responses were based on the date from when the vaccine was available to public-facing essential workers, such as healthcare workers, who were usually prioritized for vaccination in each country, not by the clinical trial dates. The vaccine developed by Astra Zeneca and the University of Oxford and the vaccine licensed by the Serum Institute of India, Covishield, were categorized as Oxford-AstraZeneca. Vaccines developed by Sinopharm with the Wuhan Institute of Biological Products or the Beijing Institute of Biological Products were not separately identified in this study.

The regional categories: The regional categories were based on countries and territories classified by the Ministry of Foreign Affairs of Japan (*4*).

The analysis items: We collected data on the vaccines used in each country and on the following five key policies: the option of vaccine type based on people's preference; vaccine eligibility for children, pregnant women, foreigners, and dignitaries under limited supply; vaccine cost; no-fault compensation programs; and regulations regarding immunization, such as voluntarily inoculation. For states that had not begun vaccination as of March, we used information about their planned or current policies or categorized them as "Do not know".

Results and Discussion

Uneven distribution of vaccine use

Figure 1 displays the vaccines by region that were in use worldwide as of March 31. Oxford-AstraZeneca was in widest use, in 112 states over 6 regions; it was much cheaper by dose, approximately 3 to 4 USD, than the vaccines based on mRNA, such as Comirnaty by Pfizer/BioNTech, which costs approximately 19 USD in the E.U. and the U.S. (*5*). Although Pfizer/BioNTech was more expensive, in March 2021, it was in use in 71 states; this might reflect that it received the earliest approval besides reflecting higher efficacy; Pfizer/BioNTech was approved on December 2, 2020, by national regulatory authorities, such as the Medicines and Healthcare products Regulatory Agency in the U.K. (*6*).

The WHO assessed that sufficient data on Pfizer/BioNTech were available for an Emergency Use Listing (EUL) recommendation on December 31, 2020 (*7*). The EUL is a procedure for assessing unlicensed vaccines, therapeutics, and *in vitro* diagnostics during PHEIC, with the goal of expediting the availability of these products to people who need them (*8*). Also, the EUL was one of the COVAX Facility's product eligibility criteria for vaccine use recommendation (*9*).

At that time, Pfizer/BioNTech required storage at -90°C to -60°C for a six-month shelf life (10), which required expensive freezers to maintain the ultra-cold temperature. Conversely, Oxford-AstraZeneca could be stored under ordinary conditions at 2-8°C (*11*). Based on its price and storage advantages, the COVAX Facility had expected that Oxford-AstraZeneca would be on EUL in the early stages.

There was uneven distribution of Pfizer/BioNTech by region. Specifically, it was used primarily in North America and Europe, where the Moderna vaccine was also in high use; both Moderna and Pfizer/BioNTech are mRNA vaccines. In December 2020, the COVAX Facility made available limited funding to support ultra-cold freezers in cases of emergency, but only 10 million USD was initially allocated (*12*). Therefore, it is highly possible that Pfizer/BioNTech was only in use in countries that could afford the vaccines and the freezers.

The U.S. government announced a donation of 500 million Pfizer/BioNTech doses for low-income countries through either the COVAX Facility or other mechanisms on June 10, 2021 (*13*), and on June 23, the COVAX Facility increased the funding for ultra-cold freezers to 775 million USD (*14*). These supports will contribute to reducing the inequitable distribution of the Pfizer/BioNTech vaccine and to increasing choice and availability in low- and middle-income countries that could not afford certain vaccines themselves.

Expanding vaccine availability

Figure 2 presents the changes in vaccine use by region from February 24, the first day the COVAX Facility delivered vaccines, to March 31. During that approximately one month, the number of states that had not started vaccination decreased from 81 to 37, and particularly in Africa, the number of states with no vaccine decreased from 40 to 16.

The COVAX Facility began vaccine delivery in

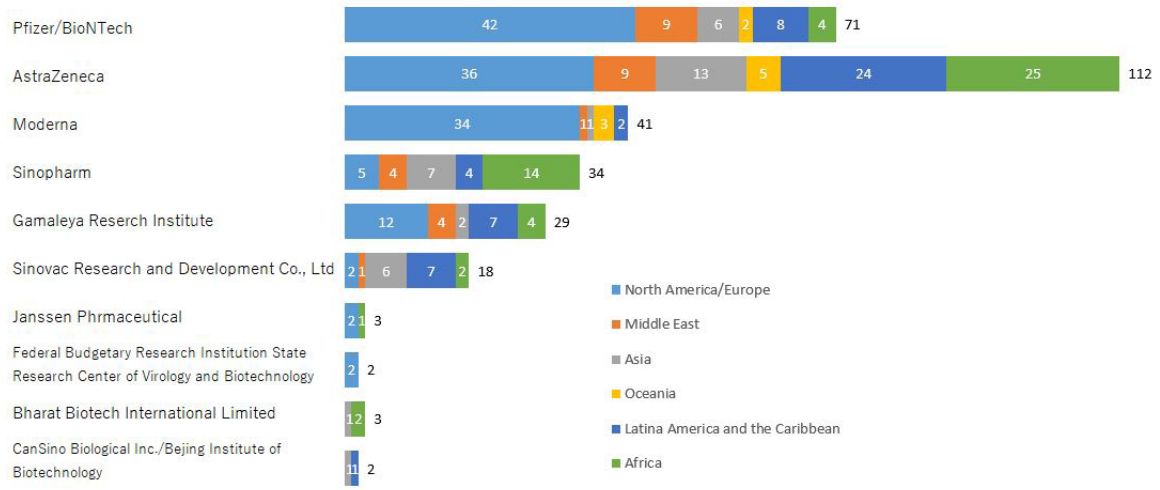

Figure 1. Nations' selected vaccines by region as of March 31, 2021.
Footnote: The figure described the number of countries or territories each vaccine was used by.

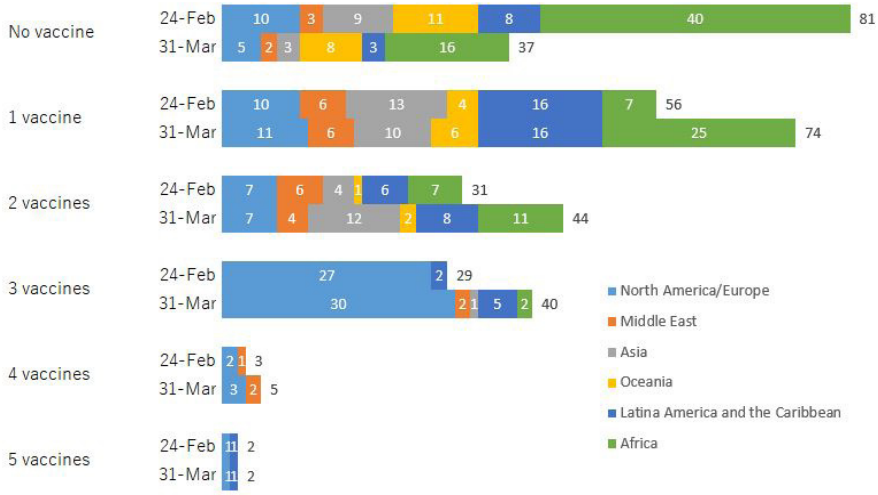

Figure 2. Changes in vaccine type and number by region between February 24 and March 31, 2021.
Footnote: The figure described the number of countries by the number of available vaccines in two time lines.

Ghana on February 24 and had reached over 100 states by April 8, 42 days later (*15*). To receive the vaccine supported by donor funding through the COVAX Facility, the states had to prepare a national vaccination plan; 92 states were eligible based on income. To develop an overall vaccination policy, a regional committee, including Gavi Independent Review Committee members, reviewed the vaccination plans of the 92 eligible economies (*16*), and because of these preparations, the vaccine administration progressed smoothly. The findings here clearly indicate that without the COVAX Facility, many more countries would not have started COVID-19 vaccination by March 31.

Overview for five vaccination policies

Supplemental Table S1 (*https://www.ghmopen.com/site/supplementaldata.html?ID=31*) presents the findings from our analyses regarding key COVID-19 vaccination policies. In most of the states (87%), people did not have a choice regarding the vaccine type they would receive, when several vaccine types were available in the country. Concerning eligibility, children were eligible for vaccination in six states as of March 2021, and 43 states recommended against COVID-19 vaccination for pregnant women. In 59 countries, foreigners could receive the vaccine under the same conditions as domestic citizens, and political leaders in 31 states had begun discussing easing quarantine restrictions for vaccinated residents. Dignitaries had received the vaccine in approximately 50% of the states. Vaccination was voluntary in 78% of the states. Only one country required residents to pay for vaccination. Forty-three states had no-fault compensation programs.

Vaccine eligibility and prioritization

The WHO Strategic Advisory Group of Experts on

Immunization used available clinical data to provide guidance for overall vaccine program strategy, including prioritization by subpopulation. Children take priority for routine immunizations; however, COVID-19 rarely causes severe illness or death in children (*17*), and in our study, six states were administering the vaccine to children as of March 2021, although some clinical data on children were available on May (*18*). Evidence showed that pregnancy was associated with increased rates of hospitalization, ICU care, and mechanical ventilation (*17*); however, the available data on vaccine use in pregnant women of the first EUL vaccine, Pfizer/BioNTech, were insufficient to assess vaccine-associated risks in relation to pregnancy as of December 2020, and the WHO was not recommending pregnancy testing prior to vaccination at that time (*10*). The initial recommendations for the COVID-19 vaccine influenced how national plans prioritized vaccination; as of March 2021, 43 states recommended that pregnant women not receive the vaccine; however, 40 states were administering the vaccine with a doctor's consultation. In June 2021, the initial recommendations for several vaccines were updated with relevant data; for example, based on its benefits, the WHO recommended the use of Pfizer/BioNTech in pregnant women (*19*).

Each country has had to prioritize vaccine distribution given limited supplies despite sufficient data showing their safety and effectiveness. Considering the inequities in vaccination rates between high- and low- to middle-income countries, countries accelerated donating vaccines through the COVAX Facility since middle of July (*20,21*). Countries with high vaccination rates, in particular, should increase dose-donation for vulnerable countries before administering booster shots for the general population in the countries, because there was limited data that booster doses were efficient in September 2021 (*22*).

No-fault compensation

Before the pandemic, no-fault compensation programs were set up in a few high-income countries; we identified 39 states with such programs for vaccine injuries, and 3 had established the programs for the COVID-19 vaccine. In a prior study in 2018, only 25 states had no-fault compensation programs for vaccine injuries, with programs administered at the central government level in 15 states (*23*). The COVAX No-Fault Compensation Program started in April 2021 to protect the 92 eligible economies (*24,25*), and the COVAX Facility requested that all participating countries make indemnification and liability agreements with each manufacturer before they shipped the vaccine (*16*). The aims of vaccine injury compensation were to promote vaccination with fair compensation for individuals in the event of harm and to accelerate vaccine research and development while protecting manufacturers from liability. The latter was especially important because the COVID-19 vaccines were developed at unprecedented speed, and there were uncertainties concerning severe adverse events or long-term effects.

COVID-19 vaccine fees

In the acute phase of an infectious disease, it is reasonable for any vaccine to be free of charge for all to promote vaccine access and prevent severe disease and death. In most of the surveyed countries, 72%, the governments administered the vaccines at no cost to the public. The COVAX Facility decided that the pledge for vaccine procurement by donors would cover at least 20% of a nation's population, excluding India because of its large population, during the acute phase of COVID-19 for the 92 eligible lower-income countries and that it would then introduce a cost-sharing mechanism both to ensure sustainability of vaccine distribution and encourage a sense of ownership (*26,27*). It is possible that COVID-19 vaccination will require a yearly booster shot in the same way as seasonal influenza vaccination and that people might need to pay for it. To avoid the situation where low-income individuals hesitate to get vaccinated or low-income countries do not purchase the vaccine, careful consideration should be given to covering out-of-pocket costs for the COVID-19 vaccine.

Vaccination regulations

The WHO stated that either governments or institutional policymakers or both should encourage voluntary vaccination against COVID-19 before contemplating mandatory vaccination (*28*). In our survey, the COVID-19 vaccination was voluntary in most states (78%). The ongoing COVID-19 pandemic is sufficiently dire that it necessitated drastic restrictions on social activity, including national lockdowns, but securing the public health had tremendous economic impacts, and the lockdowns were controversial. There were high expectations for vaccines to control COVID-19, and some national leaders focused on expanding their vaccinated populations.

For instance, most of the WHO EUL-approved vaccines, except for that of the Janssen Pharmaceutical, need two doses at intervals recommended according to clinical trial data; however, to extend access with limited supplies, some countries emphasized administering the first dose to as many people as possible before giving the second shot. For example, leaders in the U.K. elected to extend the interval between doses for Pfizer/BioNTech from 3 weeks to 12 (*29*), and similar decisions were made for Oxford-AstraZeneca, for which a longer gap between doses had shown improved efficacy in some age groups (*30*). We found only five countries prioritized to expand first shots before second shots were completed. Although governments attempted to maximize the public

health impact of the vaccine and the WHO recommended longer between-dose intervals given the limited supply of vaccine (*10,11,19*), most governments seemed hesitant to deviate from the recommended protocol and expand administration of single shots.

There was high demand from industries to reduce the COVID-19 restrictions on international mobility, especially from aviation industries, because international tourism fell by around 80% in 2020, and up to 174 million jobs were estimated to be at risk globally (*31*). However, easing restrictions carries risk of transmission, and indeed, some outbreaks occurred after quarantine restrictions were eased (*32,33*). Our survey only showed the eligibility of foreigners who were living within a given country, but some countries also offered the vaccine to foreign travelers (*34,35*). For example, the U.S. government offered travelers the Janssen Pharmaceutical vaccine, owned by Johnson & Johnson, which required only one shot (*36*). This type of vaccine tourism could increase the inequities in global vaccination because only countries with surplus vaccines can offer such services for rich people who can travel oversea given the limited global supply. Accelerating vaccination rates with policies such as longer intervals between doses before completing second shots was a sound decision with scientific evidences; however, we recommend against encouraging vaccine tourism or only easing regulations for vaccinated individuals. Such policies will only extend vaccine inequity given that few states had over 50% of their populations fully vaccinated by the end of June 2021 (*37*).

Strengths and limitations

For this study, we relied on information reported in the media and in press releases that was available by the end of March 2021 and COVID-19 conditions are changing dramatically from country to country depending on date; however, a particular strength of this study is that information was collected from people who understood the languages of original information. Although we could not produce a holistic view of the COVID-19 vaccination policies, we were able to highlight how these policies contributed to promoting and extending vaccination.

Conclusion

The suppression of economic activities, such as through restricted human movement during emergencies, is a major issue in many countries, and COVID-19 was not an exception; national lockdowns had tremendous social and economic impacts worldwide. Vaccines were considered crucial to reopening economies and lifting restrictions, and once these became available, most governments attempted to eliminate or decrease barriers to vaccination by making it voluntary and administering the vaccines free of charge. The COVAX Facility comprehensive global system and relevant vaccine policies established in each country were highly effective at ensuring equitable access to the COVID-19 vaccine and protecting people. From February 24, 2021, when the COVAX Facility distributed the first vaccines to a low-income country, to the end of March, the number of countries that had not started vaccination decreased substantially, especially in Africa; the COVAX Facility supported 46 African nations in expanding vaccine access as 92 eligible low-income countries. This review of policies worldwide and accumulated data could make substantive contributions to countries' vaccination policies. The systems for adjusting uncertainties and making justifiable policies, such as emergency use approval mechanisms and no-fault compensation programs, for vaccine injuries are of great use during this ongoing pandemic and will contribute to preparedness for the next one.

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COMMUNICATION

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Sensitivity of three antibody assays to SARS-CoV-2 nucleocapsid protein in relation to timing since diagnosis

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Abstract: The sensitivity of immunoassay for antibodies to SARS-CoV-2 may decrease over time. We compared three serology assays against SARS-CoV-2 nucleocapsid protein using serum samples of 20 health care workers with a history of mild PCR-confirmed coronavirus disease 2019 (COVID-19) at various timing since diagnosis. Overall, the sensitivity (95% confidence interval) was 95.0 (75.1-99.9), 60.0 (36.1-81.0), and 45.0 (23.1-68.5) for the Roche, Sysmex, and Abbott assays, respectively. The sensitivity of all these assays exceeded 80 for those diagnosed within 6 months, whereas it varied considerably for those diagnosed more than 6 months ago: 88.9 (Roche) versus 0 (Abbott). The present data provide a reference for researchers planning serological studies and interpreting these data. Such assay difference in terms of detection durability can be used, if used in combination, for the estimation of the timing of previously undetected infection.

***Keywords*:** COVID-19, SARS-CoV-2, immunoassay, antibody, sero-epidemiologic studies, Japan

Introduction

Epidemiological data on the spread of SARS-CoV-2 infection are helpful for planning strategies to control coronavirus disease 2019 (COVID-19). The number of COVID-19 cases confirmed by reverse-transcription polymerase chain reaction (RT-PCR), which has been performed mainly for symptomatic cases, does not represent the whole picture of this infection. In this context, serological study has been performed to assess the undiagnosed infection of SARS-CoV-2 in a population (*1*).

Several immunoassays for antibodies to SARS-CoV-2 have been developed and proved to be highly sensitive in detecting recently diagnosed cases (*2*). Due to the waning of antibodies within months, especially among those without symptoms (*3*), however, a concern has been raised about the increasing gap between seroprevalence and cumulative infection over time.

Following an earlier report that showed a variation in sensitivity among assays after 3-4 months since disease onset (*4*), several serological studies with a longer period of follow-up have demonstrated an even larger between-assay variation in sensitivity (*5-7*). Data on this issue is scarce in Asians, who recorded higher maximum anti-nucleocapsid levels after infection (*3*). Here we compared three immunoassays against SARS-CoV-2 nucleocapsid protein among health care workers with a history of COVID-19 in a Japanese hospital.

Sero-epidemiological study among health care workers

A repeat serological study has been conducted since July 2020 among workers of National Center for Global Health and Medicine (NCGM) (*8*), which has accepted many patients with severe COVID-19. We asked participants about COVID-19 related information including a history of COVID-19 and the date of diagnosis, which were confirmed against records kept by the infection control department. The current study included participants who reported a history of COVID-19 at the third survey (June 2021). Written informed consent was obtained from each participant, and the study procedure was approved by the ethics committee of NCGM.

Assessment of three antibody assays

We measured antibodies against SARS-CoV-2 nucleocapsid protein, which increased after SARS-CoV-2 infection but not after vaccination, using three commercially available kits; namely, Elecsys® Anti-SARS-CoV-2 immunoassay (Roche diagnostic),

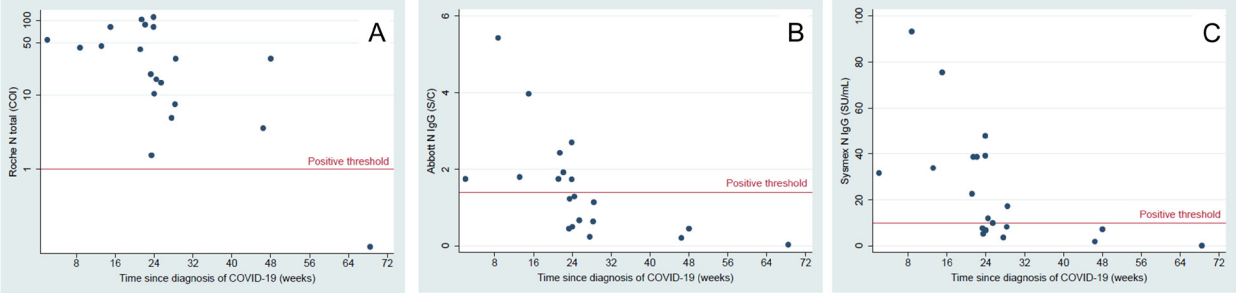

Figure 1. SARS-CoV-2 antibody titers of the Roche (A), Abbott (B), and Sysmex (C) assays with time since diagnosis of COVID-19.

Table 1. Sensitivity of three SARS-CoV-2 antibody assays according to time since diagnosis of COVID-19

Items	Timing of COVID-19 diagnosis with RT-PCR			
	Over 6 months (24 weeks) ago		Within 6 months (24 weeks)	
	No. of positives /Total number	Sensitivity (95% CI)	No. of positives /Total number	Sensitivity (95% CI)
Roche	8 / 9	88.9 (51.8 - 99.7)	11 / 11	100 (71.5 - 100)
Sysmex	3 / 9	33.3 (7.5 - 70.1)	9 / 11	81.8 (48.2 - 97.7)
Abbott	0 / 9	0 (0 - 33.6)	9 / 11	81.8 (48.2 - 97.7)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

SARS-CoV-2 IgG assay (Abbott), and HISCL anti-SARS-CoV-2 immunoassay (Sysmex). We plotted immunoglobulin titer/assay signal against time since COVID-19 diagnosis and calculated the proportion of detecting COVID-19 confirmed cases (sensitivity) for each assay according to time since diagnosis.

Identification of individuals with a history of COVID-19

Of 2,763 participants (89%) of the third survey, 20 self-reported a history of RT-PCR confirmed COVID-19, which was confirmed against the hospital record. Of these, 5 (25%) were admitted to a hospital while contracting COVID-19, but none received mechanical ventilation; 14 (70%) received Pfizer-BioNTech vaccine twice.

Comparison of seropositive rate according to the timing since diagnosis

In the Roche assay, 19 of 20 previously diagnosed COVID-19 cases showed positive, and the titer appears not to be related to the timing of diagnosis (Figure 1A). In the Abbott assay, only 9 of 20 cases were positive, and the proportion of positive cases dramatically decreased over time, with all 9 cases diagnosed more than 6 months ago being negative (Figure 1B). The Sysmex assay also showed a decreasing trend of positivity over time; 12 of 20 cases were seropositive, and two-thirds of cases diagnosed more than 6 months ago showed negative (n = 6/9) (Figure 1C).

Comparison of sensitivity according to the timing since diagnosis

Overall, the sensitivity (95% confidence interval) was 95.0 (75.1-99.9), 60.0 (36.1-81.0), and 45.0 (23.1-68.5) for the Roche, Sysmex, and Abbott assays, respectively. The sensitivity of these assays exceeded 80 for those diagnosed within 6 months, whereas it varied considerably for those diagnosed more than 6 months ago: 88.9 (Roche) versus 0 (Abbott) (Table 1).

Careful evaluation of assay is needed when planning serological studies and interpreting data in the later stages of a pandemic

In a cross-sectional analysis of health care staff with a history of COVID-19, we found a remarkable difference in the sensitivity over time among the three commercially available assays, with sensitivity being the highest in the Roche assay, followed by the Sysmex and Abbott assays.

The three assays showed a sensitivity of over 80 for the samples taken from patients who were diagnosed within 6 months. However, the Abbott and Sysmex assays, both of which are targeted for IgG SARS-CoV-2 nucleocapsid protein, showed a considerably low sensitivity for the samples taken more than 6 months after diagnosis. Similarly, long-term repeat serological studies have reported a high sensitivity of the Roche

assay but a considerably low sensitivity of the Abbott assay toward the end of follow-up (*5*-*7*).

The population studied was comprised of individuals with a history of mild COVID-19, which has been associated with lower antibody titers than severe one (*6*). Given that mild cases explain a major portion of this disease, the large between-assay difference in sensitivity observed in the present as well as previous studies highlights the need for careful evaluation of assay when planning serological studies and interpreting data in the later period of the pandemic.

We should acknowledge study limitations. First, due to the small size of the study (n = 20), the estimated sensitivities have wide confidence intervals. Second, as mentioned above, our study included only patients with mild COVID-19. The result may not be applied to severe or asymptomatic cases. Third, the cross-sectional design of the study limits our inference about the change of antibody status over time for each case.

Conclusions and future directions

The present data provide a reference for researchers planning serological studies and interpreting these data. Further, such large difference among assays in terms of detection durability can be used, if used in combination, for the estimation of the timing of previously undetected infection. More research is required to examine whether the use of multiple assays can help differentiate the impact of the recent epidemic from earlier ones.

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COMMUNICATION

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Development of the neurological simulation program e-learning version (Neuro Sim-e)

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Abstract: It is difficult to coordinate the working hours of busy clinical nurses and provide lectures, but e-learning can be used during their spare time. Therefore, this study aimed to share our experience in developing and implementing the neurology simulation program e-learning version (Neuro Sim-e). Needs analysis was conducted, and the Neuro Sim-e was developed. Four evaluation questionnaires: attention, relevance, confidence, and satisfaction (ARCS) etc., were examined. We developed the Neuro Sim-e, which consists of three scenarios. The subjects were 20 nurses. Regarding the "attention", "relevance", "reliability", and "satisfaction" of the Neuro Sim-e, 70.0%, 95.0%, 65.0%, and 90.0% of the respondents answered "rather agree" or higher, respectively. The Neuro Sim-e obtained positive feedback *via* ARCS evaluation and provided adequate results as an overall assessment. It is too early to conclude whether it is as effective as or better than a mannequin-based simulation, but this study provided learning materials that nurses could use in their spare time.

***Keywords*:** neurological nursing, simulation-based learning, e-learning

Introduction

Simulation training is rapidly being incorporated into health professional education and, recently, has ascertained efficacy as a way to foster clinical judgment capabilities (*1,2*). It is common for physicians and nurses in the field of neurology to encounter sudden change cases. A delay in response can directly lead to a life-threatening situation for the patient, so a prompt and accurate response is required. Therefore, education is required in neurology to learn various techniques, behavioral patterns, communication skills, and logical thinking in a real-world context. Conversely, in addition to the skill training, such as cardiopulmonary resuscitation, the Simulation-Based learning in the emergency field (*3,4*) and cardiovascular field (*5*), which often provide treatment for emergency changes and severe diseases, is applied sporadically. However, similarly, there is training specific to the neurology field, where the possibility of sudden patient changes is high.

It is also difficult to coordinate the working hours of busy clinical nurses and provide lectures simultaneously. Therefore, e-learning can be used "anytime and anywhere" during their spare time and can be applied when learners wish to learn. Moreover, in e-learning so far, the learning methods, such as the confirmation of knowledge, have been the mainstream, but are insufficient in improving the clinical practice ability. To compensate, Goal-Based Scenario (*6,7*) proposed by Schank is appropriate. Goal-Based Scenario (GBS) is the acquisition of necessary knowledge and skills while repeating training and error for the achievement of a given goal in the educational material using the experience of learning by failing a subject. Based on GBS, learners can learn how to make decisions by not only remembering knowledge they wish to acquire but also using that knowledge in practice.

Therefore, the aim of this short communication is to share our experience in developing and implementing a GBS-based the neurology simulation program-e-learning version (Neuro Sim-e).

Research design for developing the Neuro Sim-e

Flow of scenario creation

To develop the Neuro Sim-e, a semi-structured interview learning needs survey was administered to 10 second

year or older nurses in the neurology department of A University Hospital to determine their learning needs. The data collection period was from September 1, 2020 to March 31, 2021. The survey comprised of questions about frequent diseases and situations in clinical settings, learning needs, and barriers and needs in skill upgrading. The results of the interview survey were analysed qualitatively and inductively.

Based on need analyses, the diseases, situations, and learning components used in the case are considered among researchers. Next, seven components (mission, coverage story, roles, learning goals, scenario manipulation, feedback, and source) of GBS (*8*) are considered. The created content is set for online learning using Moodle, a learning management system. Then, researchers and three nurses with clinical experience in the neurology domain or intensive care unit confirmed content validity. Finally, a test run was performed to check whether the learning goal could be achieved and whether there was confusion or inadequacy.

The Neuro Sim-e evaluation

Subjects

The selection criteria for the study subjects were staff nurses who were assigned to the Department of Neurology at the University Hospital B in Japan and were in their second year or older who agreed to participate in this study. Exclusion criteria were qualified nurses such as certified nurse specialists.

Survey contents

The survey consisted of the attention, relevance, confidence, and satisfaction (ARCS) (9) evaluation questionnaire of Kirkpatrick's four-level training evaluation model (*10*). For level 1 response, four items were investigated. The answers were measured on a four-point Likert scale: 4 for "I think so" and 1 for "I do not think so".

Moreover, the Neuro Sim-e evaluation questionnaires consisting of five items (including one free-text), and learning time and rate of correct answers, as Kirkpatrick's four-level training evaluation model level 2 learning were investigated. The degree of difficulty, amount of questions, whether knowledge that can be used in practice was acquired, and whether they felt that they could use it in practice were asked in the Neuro Sim-e evaluation questionnaire. It also included an open-ended section for the user to express positive feedback and areas for improvement.

Survey method

The researcher asked all 25 candidates to participate in this study verbally and in writing. Consent to participate in this study was obtained by accessing the Neuro Sim-e on Moodle and responding to the presence or absence of consent. When accessing the Neuro Sim-e, the ID and password were prepared and shared with the subject.

Data analysis

The ARCS evaluation questionnaire and the Neuro Sim-e evaluation sheet were used to perform descriptive statistics. The Neuro Sim-e was used for learning analysis. Moreover, free description of the Neuro Sim-e evaluation sheet was analysed qualitatively and inductively.

Ethical considerations

This study was conducted with approval from the Research Ethics Committee of the Graduate School of Nursing, Nagoya City University (approval number: 18034). The subjects received verbal and written explanations about the purpose, methods, protecting personal information, e-learning, and responding to the questionnaire to ensure that individuals are not identified by their shared IDs and passwords.

Core elements of the Neuro Sim-e

The Neuro Sim-e development

As a result of the learning needs analysis, eight categories regarding the most frequent diseases and situations in clinical settings, and eight categories regarding barriers and necessities for skill upgrading were extracted (Table S1, *https://www.ghmopen.com/site/supplementaldata.html?ID=52*).

Based on the results, it was determined that the case needed to include the situations of "response to endovascular surgery" and "deterioration of condition after surgery", and was classified into three events: *i*) carotid artery stenting (CAS) in the posterior carotid sinus reflex, *ii*) CAS in posterior hypoperfusion syndrome, and *iii*) post-craniotomy cerebral infarction. The three situations were classified as observation, implementation of nursing care, and evaluation. Moreover, seven components of GBSs were considered. As an example, the GBS component of Case 1 is shown in Table S2 (*https://www.ghmopen.com/site/supplementaldata.html?ID=52*). The contents were set for online learning using Moodle, a learning management system.

Overview of study subjects

Requests were sent to 25 nurses, and 20 responses were obtained (80.0% response rate) from 18 women and 2 men in the neurology department at B University Hospital. The educational background of the subjects was as follows: junior college for 2 subjects, university for 16 subjects, and master's degree for 2 subjects. A total of 12 subjects had 3-5 years of nursing experience, 4 had 6-10 years, and 4 had ≥ 11 years. The Neuro

Table 1. ARCS evaluation questionnaire

Items	Four-level training evaluation				*n* = 20 Mean ± SD
	1 I do not think so *n* (%)	2 I somewhat do not think so *n* (%)	3 I somewhat think so *n* (%)	4 I think so *n* (%)	
Attention	1 (5.0)	5 (25.0)	12 (60.0)	2 (10.0)	2.75 ± 0.72
Relevance	0 (0.0)	1 (5.0)	17 (85.0)	2 (10.0)	3.05 ± 0.40
Confidence	1 (5.0)	6 (30.0)	0 (0.0)	13 (65.0)	2.60 ± 0.60
Satisfaction	0 (0.0)	2 (10.0)	15 (75.0)	3 (15.0)	3.05 ± 0.41

ARCS: attention, relevance, confidence, and satisfaction.

Sim-e and the ARCS evaluation questionnaire were administered to all 20 subjects who agreed to participate in the study.

The Neuro Sim-e evaluation

Kirkpatrick's four-level training evaluation model: Level 1 response

In terms of "Attention", "Relevance", "Confidence", and "Satisfaction" for the Neuro Sim-e the number of respondents that answered "I somewhat think so" or more, "Confidence" was slightly low (Table 1).

"Degree of difficulty", "Amount of questions" of five-item questions for the Neuro Sim-e evaluation were negatively answered. "Whether knowledge that can be used in practice was acquired" and "whether they felt that they could use it in practice" were positively answered (Table 2).

Free-text results were also summarized in 30 codes and 9 categories. Below, categories are indicated by the strongest quote. On the case used in the Neuro Sim-e, the opinion of "It was real cases and practice contents" was obtained. In addition, positive answers such as "I was able to deepen my knowledge", "I was able to learn how to report", "I want to put learning into practice", and "I learned how to deal with sudden changes" were reported. On the other hand, there were opinions on content and methods, such as "The descriptive test was difficult", "The number of free descriptions were many and it took a lot of time", "Difficult to see test", and "Difficult to perform with devices other than PC".

The ARCS evaluation for the Neuro Sim-e showed positive results. Therefore, it can be said that the learning motivation for the Neuro-Sim-e was effective. In a previous study on self-learning of neurological e-learning conducted in Korea (*11*), it was found that nurses' neurological assessment skills were improved. From this, it can be said that e-learning materials are an effective method for improving nurses' judgment and assessment skills. Moreover, the Neuro Sim-e is a GBS-based program, intended to not only remember the knowledge to be acquired but also to learn how to judge by utilizing that knowledge. From the result of this study, it was not only possible to deepen the knowledge but also to learn how to deal with and report the sudden change. It was evaluated that the learning which reflected the philosophy of GBS was possible and considered to be a great achievement.

Table 2. Neuro Sim-e evaluation questionnaire

Items	*n*	%	Mean ± SD
Degree of difficulty			1.85 ± 1.01
Difficulty	11	55.0	
A little difficulty	3	15.0	
Just right	4	20.0	
A little easy	2	10.0	
Easy	0	0.0	
Amount of questions			1.20 ± 0.41
Many	16	80.0	
A little more	4	20.0	
Just right	0	0.0	
A little few	0	0.0	
Few	0	0.0	
Whether knowledge that can be used in practice was acquired			3.10 ± 0.72
Acquired	6	30.0	
A little acquired	10	50.0	
Not acquired a little	0	0.0	
Not acquired	4	20.0	
Whether they felt that they could use it in practice			3.00 ± 0.46
I think so	2	10.0	
I somewhat think so	16	80.0	
I somewhat do not think so	2	10.0	
I do not think so	0	0.0	

However, it was suggested that the following points need to be improved. First, of the four items of the ARCS evaluation, "Confidence" was lower than the other three items, so further improvement is needed. High results are obtained for "Confidence" in Western studies (*12*), but "Confidence" tends to be low in previous studies in Japan (*13,14*). Therefore, it is considered that there is a Japanese cultural background of humility. Second, regarding the evaluation of the Neuro Sim-e, the difficulty level was high. This finding should be improved, and the high difficulty level may have influenced the inadequate "Confidence" of ARCS evaluation. Finally, participants also reported many questions and difficulty in inputting descriptive questions about reporting methods. As has been pointed

out, the circumstances used by learners have a major effect on e-learning; it will be improved by considering the ease of answering on various devices and asking multiple-choice questions. Particularly, the feature of this study is that busy clinical nurses can apply e-learning "anytime and anywhere" during their spare time and can obtain knowledge when they wish to. Therefore, it is important for it to be easily accessible on devices other than PCs.

Kirkpatrick's four-level training evaluation model: Level 2 learning

The correct answer rates for the total scores of cases 1 to 3 were 73.0%, 87.5%, and 80.4%, respectively, and Case 1 was slightly lower. The average response time (range) was 34.22 (9.12-120.55) min, 30.58 (6.30-60.85) min, and 30.35 (11.12-90.25) min, respectively.

Since this is a basic study prior to intervention research, and the goal was not to perform a pre-post comparative test of the mean points of each case, this result was an appropriate outcome as an overall overview. In Kirkpatrick's four-level training evaluation model, level 2 learning, is likely to exhibit an example of what has been experienced so far and the possibility of obtaining new findings and adapting the knowledge gained to practice. Merrill's first principle of instructional design states that "Learning is facilitated in situations where new knowledge can be used in practice" (*14*). In addition to learning content based on previous experiences, new findings and learning that can be used in actual clinical settings have been reflected in the total rating. Based on the above, the Neuro Sim-e had a certain effect on the improvement of knowledge and clinical judgment ability required for nursing in the neurology domain in Kirkpatrick's four-level training evaluation model level 1 response and level 2 learning.

Limitations

In this study, the pre- and post-comparison were insufficient, and levels 3 and 4 of Kirkpatrick's four-level training evaluation model were not evaluated. In the future, it will be necessary to add results, such as level 3 behavior and level 4 learner behavioral changes and clinical outcomes, to the evaluation items to conduct an effect confirmation study.

Conclusion

It is too early to conclude whether it is as effective as or better than a mannequin-based simulation because this is an exploratory study, but it provided learning materials that busy nurses could use in their spare time; thus, this study was meaningful.

As a result of levels 1 and 2 in Kirkpatrick's four-level training evaluation model, the effectiveness of the program could be confirmed. Conversely, from the evaluation of the Neuro Sim-e, it was suggested to refine the high degree of difficulty, quantity of questions, and convenience for use on various devices.

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LETTER

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Global extension of Japanese medical products related to COVID-19: A survey of WHO Emergency Use Listing

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Abstract: The World Health Organization (WHO) has been utilizing Emergency Use Listing (EUL) to expand access to medical products during the COVID-19 pandemic. EUL is a risk-based procedure for assessing and listing unlicensed vaccines, medicine, and *in vitro* diagnostics. To determine whether Japanese medical products acquired EUL relating to COVID-19, we conducted desk research as a part of a new project. Results showed that thirteen of twenty-eight *in vitro* diagnostic products were from China and three of ten vaccines on EUL were from India. However, only one vaccine manufactured in Japan was on EUL. A common weakness of Japanese companies in the global public procurement market was a lack of knowledge on qualification systems for medical products. We hypothesized holistic approaches from private companies and systematic supports from public sectors are required for a response to an emergency. These activities could lead to contribute to global health issues through sustainable businesses.

Keywords: global public procurement, vaccines, medicine, *in vitro* diagnostics, public-private partnership, international cooperation

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a Public Health Emergency of International Concern (PHEIC) in January 2020 (*1*). In response to the pandemic, the development of medicines, vaccines, and *in vitro* diagnostics for COVID-19 began worldwide. The Emergency Use Listing (EUL) is a WHO procedure for assessing unlicensed medicines, vaccines, and *in vitro* diagnostics during a PHEIC to expedite the availability of these products to people who need them (*2*). The EUL was established and reformed by the Emergency Use Assessment and Listing mechanism which was developed to respond to the 2014-2016 Ebola virus disease outbreak (*3*). The EUL indicates certain standards for interim use of unlicensed products under emergencies. Therefore, pharmaceutical companies were competing for the development of COVID-19 products and submitting their product documentation for EUL to supply their products worldwide. However, before submitting documentation, the establishment of an assessment platform is necessary among the WHO, external experts, and the national regulatory authority (NRA) where the products produce. The EUL procedure is based on a public-private partnership.

The number of new COVID-19 cases in Japan was very low on the week of December 22, 2021, with about 0.9 per 100,000 and no cases in some regions (*4*). However, Japan also had the first report of a new SARS-CoV-2 variant belonging to the Pango lineage B.1.1.529 (Omicron variant) on December 6, which has spread rapidly in January (*5*). The number of new COVID-19 cases in Japan increased to 41 per 100,000 on the week of January 13, 2022 (*6*). The Omicron variant has been spreading rapidly around the world and 20 million new cases globally were confirmed on the week of January 10 (*7*). Considering the ongoing pandemic, the EUL should be continuously used to expand access to COVID-19 medical products.

The Bureau of International Health Cooperation, National Center for Global Health and Medicine (NCGM) conducted the preliminary result of a desk research to examine whether Japanese medical products acquired EUL relating to COVID-19.

By January 17, 2022, the Pharmaceutical and Medical Devices Agency (PMDA) responsible for approval of medicine or medical devices relating to COVID-19 in Japan approved 71 *in vitro* diagnostic products, 3 vaccines, and 5 medicines including special

approval which distributed by companies in Japan (*8*). Meanwhile, 28 *in vitro* diagnostic products, 10 vaccines, and no medicines were listed on the EUL (Figure 1).

Table 1 shows the countries of origin of developers who applied to EUL and were accepted on the list. In Table 1, we counted vaccines by the number of national authorities instead of the number of countries that developed the product because if the same vaccine was manufactured in other countries, a different application to EUL with each national authority's platform was still needed. *In vitro* diagnostic products by Chinese companies were the most frequently accepted among 74 applications to EUL, followed by American companies. Vaccines by Indian companies were the most frequently accepted among 29 applications on EUL, followed by China, the U.S., Korea, and the Netherlands. Half as many vaccine applications compared to *in vitro* diagnostics for EUL were listed by January 17, 2022. This may reflect the complexity of products and the assessment process for vaccines (*9*), while there were 140 vaccine candidates in clinical trials in the world (*10*).

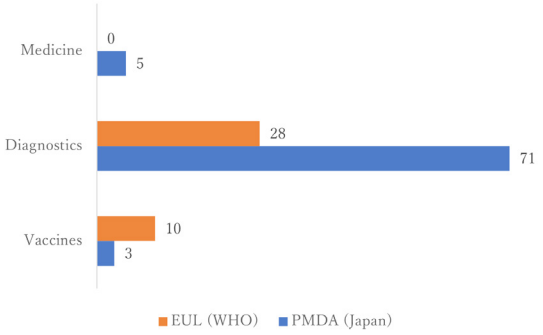

Figure 1. The number of medical products related to COVID-19 by qualification as of January 17, 2022 (date of data accession). Data are updated irregularly. PMDA: Pharmaceutical and Medical Devices Agency of Japan; EUL: Emergency Use Listing by World Health Organization.

Forty-eight products from China underwent application for the EUL, which is four times that from the U.S., although the acceptance proportion in China was much lower than that for U.S. products (Table 1). This may be a result of the "Made in China 2025 (MIC25)" policy (*11*). The MIC25 policy was launched in 2015 by Xi Jinping, the party and state leader of China. The strategy defined ten core industries, including biomedicine and high-performance medical equipment aimed at boosting local capabilities. Furthermore, more than 1,800 government industrial investment funds were invested in MIC25 with 3 trillion CNY in March 2018 (*11*). MIC25 encourages the development of key biopharma clusters to accelerate innovative research and clinical trials (*12*).

Table 1. The number of products categorized by the countries of origin of product developers on Emergency Use Listing as of January 17, 2022 (date of data accession)

Countries	Diagnostics (Total: 74)		Vaccines (Total: 29)			
	Accepted	Not accepted	Accepted (The name of vaccine)	In process	Total	Acceptance proportion (%)
China	13	28	2 (Coronavac, ShinophamBIBP)	5	48	31
United States	7	2	2 (Comirnary, Spikevax)	0	11	82
India	1	3	3 (Covishield, Covaxin, Covovax)	1	8	50
Korea	3	3	2 (Vaxzevria, Spikevax)	0	8	63
Germany	2	3	1 (Comirnaty)	0	6	50
United Kingdom	1	1	0	0	2	50
Japan	0	1	1 (Vaxzevria)	0	2	50
Netherlands	0	0	2 (Ad26.COV2-S, Nuvacovid)	0	2	100
Turkey	1	1	0	0	2	50
Vietnam	0	2	0	0	2	0
Italy	0	2	0	0	2	0
Russia	0	0	0	2	2	0
Spain	0	0	1 (Spikevax)	0	1	100
Australia	0	0	1 (Vaxzevria)	0	1	100
Sweden	0	0	1 (Vaxzevria)	0	1	100
France	0	0	0	1	1	0
Cuba	0	0	0	1	1	0
Canada	0	0	1 (Vaxzevria)	0	1	100
Mexico	0	0	1 (Vaxzevria)	0	1	100
Argentina	0	0	1 (Vaxzevria)	0	1	100
Total	28	46	19	10	103	

Footnote: Comirnaty was developed by BioNTech (Germany) and Pfizer (United States). Vaxzevria was developed by AstraZeneca and Oxford University in the United Kingdom. Spikevax was developed by Moderna Biotech (United States). We assigned each vaccine to its respective national authority listed on Emergency Use Listing. Vaccines approved by the European Medicines Agency (EMA) were assigned to the country or countries which applied to the EMA. There were many *in vitro* diagnostic products under review, which numbers were not counted in Table 1. We calculated the acceptance proportion based on our definition for this survey based on the latest available data from January 17, 2022. Data are updated irregularly.

Japanese companies rarely competed to apply for EUL, although there are 71 PMDA-approved *in vitro* diagnostic products in Japan. Only one vaccine produced by Japanese companies was on the EUL list, which was developed by AstraZeneca and Oxford University (*13*). Recent surveys showed that one of the common weaknesses of Japanese companies in the global public procurement market was a lack of knowledge about the qualification procedure for medical products (*14*) and a lack of understanding of global public procurement systems (*15*). Language barriers should also be considered. To fill the gap, the NCGM has implemented a series of seminars to introduce the qualification procedure, focusing on "prequalification" (PQ) as defined by the WHO. PQ is a systematic process to determine the capacity of a manufacturer to produce medical products of consistent quality in accordance with WHO specifications (*16*), which is utilized for general procurement. Compared with PQ, EUL focuses on only three categories of products (vaccines, medicines, *in vitro* diagnostics) for emergency procurement. The series of seminars related PQ is a part of activities supported by the projects for the global extension of medical technologies which have implemented since 2015 under the "Japan Revitalization Strategy" by the Government of Japan (*17*). These projects aim to disseminate Japanese medical technologies, high-quality medicines, medical devices, and health services in a way that suits local needs and to improve health and medical care in low- and middle-income countries. The project detail was available on the other paper (*17*).

Under the project newly granted from 2021 to 2023, we have analyzed the process for both global public procurement and emergency procurement related to COVID-19 and hypothesized that seven steps based on "the access and delivery partnership" approach are essential for both means of procurement (*18*). The seven steps are as follows: *i*) analysis of needs, *ii*) research and development, *iii*) regulatory approval, *iv*) selection and prioritization, *v*) procurement or bidding, *vi*) distribution and storage, and *vii*) service delivery. The integrated approach across the seven steps by private companies is necessary to drive successful global public procurement. We are continuing analysis of case studies to find out root causes and possible solutions or public-private interventions for joining the global public procurement and for quickly responding to global emergency procurement.

Only one vaccine produced by Japanese companies had EUL, which was developed by AstraZeneca and Oxford University. Moreover, Japanese companies seem to not be successful when applying for general global public procurement related to COVID-19 (*19*). Several successful Japanese companies for global public procurement under COVID-19 were continuously preparing before the pandemic. To encounter current and future public health emergencies, basic preparation for global public procurement will help during emergency procurement procedures including applying to EUL. Further systematic supports from the public sectors to private companies are needed to enter the global public procurement market. The Government of Japan established the "Global Health Strategy Promotion Council" under the Prime Minister of Japan and the Cabinet to strengthen global health strategy in 2021 (*20*). Japan will determine how they can contribute to global health issues through enhancing sustainable business and public-private partnerships.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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LETTER

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The state of foreigners living in Japan as gauged by people undergoing a comprehensive health checkup (Ningen Dock)

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Abstract: Benefiting from the Japanese Government's welcoming of foreign visitors, our facility was able to accept and respond to large number of foreign tourists (1,493) to undergo a comprehensive health checkup (Ningen Dock) in 2019. However, coronavirus disease 2019 (COVID-19) completely precluded the acceptance of tourists for two years starting in from 2020. In August 2020, our hospital policy was changed to actively accept foreign residents in Japan for comprehensive health checkups. In this article, we analyzed the foreign residents who use our facility in detail and we investigated the characteristics of foreign residents from the viewpoint of a comprehensive health checkup.

***Keywords*:** Ningen Dock, foreign residents, female consultation rate

The number of foreigners residing in Japan was 2,760,635 (*1*) at the end of 2021, and it has decreased every year since 2019. Dividing the number of foreign residents by the current latest total population of Japan (*2*) gives approximately 2.20%. Foreign residents accounted for 2.32% of the population in Japan in 2019 but gradually decreased to 2.29% in 2020 and 2.20% in 2021. This suggests that the number of foreign residents is decreasing. In 2019, the number of foreign residents reached its peak, and the tourism industry was at its peak. However, the COVID-19 pandemic that started in the beginning of 2020 has presumably affected the number of foreign residents.

Looking at the number of foreign residents by nationality, most are Chinese, but that proportion is lower than it was in 2017. The number of Vietnamese living in Japan is on the rise, surpassing Koreans in 2020 and accounting for the second largest proportion after Chinese.

Benefiting from the Japanese Government's welcoming of foreign visitors, the authors' facility was able to accept and handle a large number of foreign tourists (1,493) undergoing a comprehensive health checkup (Ningen Dock) in 2019 (*3*). However, COVID-19 completely precluded the acceptance of tourists for two years starting in 2020. Therefore, hospital policy was changed in August 2020 to actively accept foreign residents in Japan for comprehensive health checkups, and the collection of statistics on foreign residents started at the same time.

Here, the foreign residents visiting this facility have been analyzed in detail while referring to data from the Immigration Bureau and the Statistics Bureau, and the characteristics of foreign residents have been investigated from the viewpoint of a comprehensive health checkup.

This facility accepted 159 foreign residents living in Japan from August 2020 to December 2021. The 159 foreigners included 96 Chinese, 24 Koreans, 8 Vietnamese, 6 Americans, 4 French, 3 Canadians, 2 Bangladesh, 2 British, 2 Philippines, 2 Bulgarians, 2 Germans, 1 Thai, 1 Swiss, 1 Israeli, 1 Mongolian, 1 Kenyan, 1 Brazilian, 1 Singaporean, and 1 Peruvian (Figure 1). Foreigners were from a total of 19 countries. According to statistics from the Immigration Bureau (*1*), the largest proportion of foreign residents in Japan is from China (26.0%), followed by Vietnam (15.7%), South Korea (14.8%), Philippines (10.0%), and Brazil (7.4%). People undergoing a comprehensive health checkup at the authors' facility were from China (60.4%), South Korea (15.1%), Vietnam (5.0%), the United States (3.8%), and France (2.5%). Although these numbers are roughly proportional to the foreign population, many of the people undergoing a comprehensive health checkup were Chinese, suggesting that Chinese are highly interested in comprehensive health checkups or their health.

Foreign residents undergoing a comprehensive health checkup consisted of 52.2% males and 47.8% females, with an average male age of 43.6 years and an average female age of 43.0 years. The male-female ratio of all the people undergoing a comprehensive health checkup (almost 96% Japanese) in 2021 was 57.7% males with

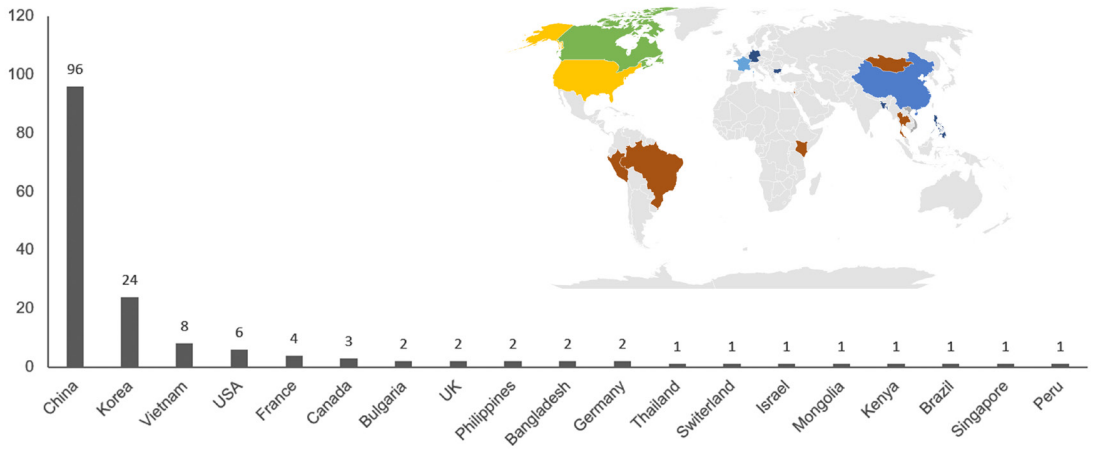

Figure 1. Number of foreigners undergoing a comprehensive health checkup (Ningen Dock) in Japan by their country of origin (Aug. 2020 – Dec. 2021).

an average age of 54.6 years and 42.3% females with an average age of 53.5 years. Compared to all of the people undergoing a comprehensive health checkup, the female consultation rate was higher for foreign residents and those residents were 10 years younger on average. This suggests that young female foreign residents are more interested in comprehensive health checkups than Japanese.

Of the total of 4,178 people undergoing a comprehensive health checkup, 159 (3.8%) were foreign residents and 51 (32.1%) needed language support. By country, 32 (33.3%) of the 96 Chinese needed language support. One (4.2%) of the 24 Koreans and 5 (62.5%) of the 8 Vietnamese needed language support. Of the 31 foreigners from 16 countries other than China, South Korea, and Vietnam, 13 (41.9%) needed English support. Koreans are less likely to need language support and are likely to be more familiar with Japanese society. That said, the number of Vietnamese residents has increased rapidly, and many of the residents needed language support during a consultation. About 30% of foreign residents appear to be fluent in Japanese and they can function in everyday life but they are worried about medical terms and need a medical interpreter.

Since medical terms in specialized fields are complicated and informed consent is important in medicine, the demand for medical interpreters is expected to increase in the future. In order for foreign residents in Japan to safely and comfortably receive medical care, many issues need to be addressed, such as training, evaluation, and employment of medical interpreters.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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