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Mix-and-match COVID-19 vaccination: a proper strategy for countries of COVID-19 vaccine shortage

Abstract

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienDirect, PubMed, Scopus, and ISI Web of Science. The search was applied to the articles that were published between January 2021 and November 2021. With strict literature search and screening processes, it yielded 10 articles from 136 articles of initial literature database. In June 2021, a preliminary study conducted by the University of Oxford scientists demonstrated that mixing the AstraZeneca and Pfizer vaccines produced a robust immune response against the SARS-CoV-2 (COVID-19) virus and induced higher antibodies than an only two-dose schedule of AstraZeneca vaccine and none of the groups demonstrated decreased neutralizing activity against the Alpha variant (UK variant), but the neutralization titer reduced by 2.5 to 6times against the Beta variant (South African variant), Gamma variant (Brazilian variant), and Delta variant (Indian variant). The Comparing COVID-19 Vaccine Schedule Combinations (Com-COV) study (463 cases of the 4-week interval group) revealed that immunization with AstraZeneca vaccine followed by Pfizer vaccine at the 4-week interval demonstrated a better immune response out of the two mixed dosing regimens. Com-COV study demonstrated in the earlier phase that around 30 % to 40 % of those who received mixed doses reported fevers after their second jab, compared to 10 % to 20 % of those who received the same vaccine for both doses. This result could be attributable to the shorter, 4-week interval between doses that was used during the Oxford study, whereas the safety data from a cohort with a 12-week dosing interval is still to appear.

In conclusion, it is better to give a different COVID-19 vaccine or mix-and-match COVID-19 vaccination than not administer the second dose at all.

Keywords: COVID-19, mix-and-match, mix, match, vaccine, vaccination

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Abbreviations: Com-COV, COVID-19 vaccine schedule combinations; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; SARS-CoV-2, Severe acute respiratory syndrome-coronavirus type 2; UK, united kingdom; USA, united states of america

Objectives of the study

The objectives of this study is aimed to identify the feasibility of mixing and matching COVID-19 vaccination in the situation of shortage of COVID-19 vaccines.

Methods of the study

Search strategy and inclusion criteria

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienDirect, PubMed, Scopus, ISI Web of Science, and websites of the news. The search was applied to the articles that were published between January 2021 and November 2021. Our first involved performing searches of article abstract/keywords/title using strings of [(“ Mix-and-match covid-19 vaccination ” or “ Mixing and matching ”, “ Vaccination ” and “ COVID-19 ”]. After a first approach of search, published articles focusing on COVID-19 were retained and the information on vaccine type and COVID-19 was extracted for having a crude knowledge involving their themes. Another round of publication search was conducted for adding the missing published articles that were not identified by the first round.

All keywords combinations from one disease type and climatic variable to bind the population of cases under consideration. Search string for disease groups include [“ SARS-CoV-2 ” or “ COVID-19 ” or “ Vaccination ” or “ Vaccines ” or “ Mixing and Matching ” or “ Mix-and-Match ”]. The initial literature databases were further manually screened with the following rules : 1) non-human infectious disease-related articles were excluded; 2) articles that did not report mix-and-match vaccination related to COVID-19 were not considered, such as commentary articles, or editorial; 3) non-peer reviewed articles were not considered to be of a scholarly trustworthy validity; and 4) duplicated and non-English articles were removed. The articles were carefully selected to guarantee the literature quality, which is a trade-off for quantity.

With strict literature search and screening processes, it yielded 10 articles from 136 articles of initial literature database. Needed article information was extracted from each article by : 1) direct information including journal, title, authors, abstract, full text documents of candidate studies, publishing year; 2) spatial scale and place name of the study area; 3) study period; 4) research method used; 5) type of COVID-19 vaccine studied; 6) types of mix-and-match vaccination studied; and 7) the conclusions made about the impacts of mix-and-match COVID-19 vaccination types on patients’ COVID-19 outcomes.

Introduction

In low-income and middle income countries, Ebola vaccine (Johnson & Johnson) experience demonstrated that mix-and-match

vaccination is feasible, safety, and long-lasting immunization, adopted in phase I and phase II trials and can overcome easily with active community participation and suitable national planning.[1,2] In addition to Ebola, this concept has been previously implemented for influenza, malaria, and HIV.[2] The prime dose in the most of the current vaccination regimen is at a month interval followed by a second homologous booster dose.[3] Recent interest in COVID-19 mixing vaccination is aimed to simplify countries' facing fluctuation of various vaccine supplies and immunization efforts and increase SARS-CoV-2 (COVID-19) protection by delivery of the similar or same antigens of the disease-causing agent via two different vaccine types and eliciting a strong and long-lasting immune response as compared to the single vaccine regimen, but has a lack of evidence and a potential risk of increased-mixing-vaccine-adverse side effects[3] that include increased headache, increased fever, increased malaise, increased joint pain, and increased AEFI, particularly in the elderly population.[3]

Results

With strict literature search and screening processes, it yielded 10 articles from 136 articles of initial literature database. Needed article information was extracted from each article by : 1) direct information including journal, title, authors, abstract, full text documents of candidate studies, publishing year; 2) place name of the study area; 3) study period; 4) research method used; 5) type of mix-and-match COVID-19 vaccination studied; and 6) the conclusions made about the yields of mix-and-match COVID-19 vaccination on human protection of COVID-19. Seven published articles in this study revealed strongly support the benefit of the mix-and-match COVID-19 vaccination by increasing the neutralizing antibody levels and number of T-cell reactivity (such as, strongly neutralizing antibody against prevalent strain B.1.1.7 with heterologous prime boost was approximately 3.9-times higher than in those receiving homologous Pfizer vaccination; number of CD4+ and CD8+ T cells reacted to SARS-CoV-2 (COVID-19) spike peptide stimulus).

Discussion

In June 2021, a preliminary study conducted by the University of Oxford scientists demonstrated that mixing the AstraZeneca and Pfizer vaccines produced a robust immune response against the SARS-CoV-2 (COVID-19) virus and induced higher antibodies than an only two-dose schedule of AstraZeneca vaccine and none of the groups demonstrated decreased neutralizing activity against the Alpha variant (UK variant), but the neutralization titer reduced by 2.5 to 6times against the Beta variant (South African variant), Gamma variant (Brazilian variant), and Delta variant (Indian variant).[4] The Comparing COVID-19 Vaccine Schedule Combinations (Com-COV) study (463 cases of the 4-week interval group) revealed that immunization with AstraZeneca vaccine followed by Pfizer vaccine at the 4-week interval demonstrated a better immune response out of the two mixed dosing regimens.[4] Com-COV study demonstrated in the earlier phase that around 30 % to 40 % of those who received mixed doses reported fevers after their second dose, compared to 10 % to 20 % of those who received the same vaccine for both doses. This result could be attributable to the shorter, 4-week interval between doses that was used during the Oxford study, whereas the safety data from a cohort with a 12-week dosing interval is still to appear.[4]

The trials in Germany and Spain have also demonstrated that a mixed dosing regimen induced a better immune response than getting two doses of the AstraZeneca vaccination.[4] In South Korea, the study on 100 actually-receiving-mixed-doses cases out of 499 cases conducted by the Korea Disease Control and Prevention Agency on a mixed vaccination, with AstraZeneca vaccine as the first dose and Pfizer vaccine as the second dose revealed the increased neutralizing antibody levels of 6times higher than those found after two doses of the AstraZeneca jab.[4] Initial phase of Com-COV study or Com-COV1 study has been concentrated on mixing the AstraZeneca and Pfizer doses, whereas Com-COV2 study or phase 2 of the Com-COV study is assessing the immunogenicity and safety of combining the Moderna and Novavax vaccines with a first dose of either the Pfizer or AstraZeneca jab.[4] Globally, COVID-19-dose-mixing studies on assessing other vaccine combinations are also ongoing, including a Russian trial of an AstraZeneca-Sputnik V combinations and a Philippines-based study mixing Sinovac' s CoronaVac vaccination with 6 other vaccines.[3] In India, COVID-19 mixing vaccination can assist in scaling up the vaccination drive to a large extent in this world's-largest-COVID-19-vaccination-drive country.[3]

As of June 6, 2021, China, UK, and USA have began the COVID-19-vaccine mixing trials, but have not yet officially approved them due to not being designed to assess actual COVID-19 protection and non-corresponding-COVID-19-real-life protection of the studies' antibody and T-cell measurements, whereas only Canada, Denmark, France, Germany, Norway, and Sweden implemented mixing vaccination to their citizens with rarely reported ChAdOx1 nCoV-19 (AstraZeneca) thromboembolic complications.[3,5] Whenever it is impossible to provide a second dose of COVID-19 vaccine, the Public Health of England guidelines recommend that it is better to give a different COVID-19 vaccine than not administer the second dose at all.,[3] On July 12, 2021, the WHO's chief scientist has suggested individuals against mixing and match in COVID-19 vaccines from different manufacturers.[6]

Nevertheless, on July 13, 2021, Thailand defended mixing two different COVID-19 vaccines to fight against a surge in SARS-CoV-2 (COVID-19) infections since COVID-19 outbreak in April 2021 after the WHO's top scientist warned that it was a " dangerous trend " not backed by evidence.[5,7] Thailand's health authorities will mix a first dose of the Chinese-produced " Sinovac " vaccination with a second dose of Astrazeneca vaccine to try and achieve a " booster " effect in 6weeks instead of 12weeks due to fast spreading disease (more than 353,700 reported- COVID-19-infected cases and 2,847 reported-COVID-19-related deaths in April 2021).[7] Figure 1,[8] Table 1[8] and 2[3] demonstrate different platforms of COVID-19 vaccines and mechanisms of antigen presentation, advantages and disadvantages of various platforms of COVID-19 vaccines, and recently published clinical trials and ongoing clinical trials on mixing COVID-19 vaccination(as of July 11, 2021), respectively.

Epidemiologists from Umeå University in Sweden analyzed their country's data of COVID-19 and revealed that compared with unvaccinated people, 68 % of those on a mixed vaccination schedule were less likely to develop a symptomatic infection, whereas the 430,000 people with two doses of AstraZeneca vaccination were 50% less likely to have symptomatic infection. It clear that the heterologous regimens are more effective than two doses of AstraZeneca vaccination. Epidemiologists from the State Serum Institute in Copenhagen, Denmark identified that one dose of AstraZeneca vaccination followed by one dose of Pfize/BioNTech vaccination was 88% effective at preventing SARS-CoV-2 (COVID-19) infection, the effectiveness similar to that of two doses of Pfizer vaccination. Denmark stopped all use of the AstraZeneca vaccine in April 2021.[9,10]

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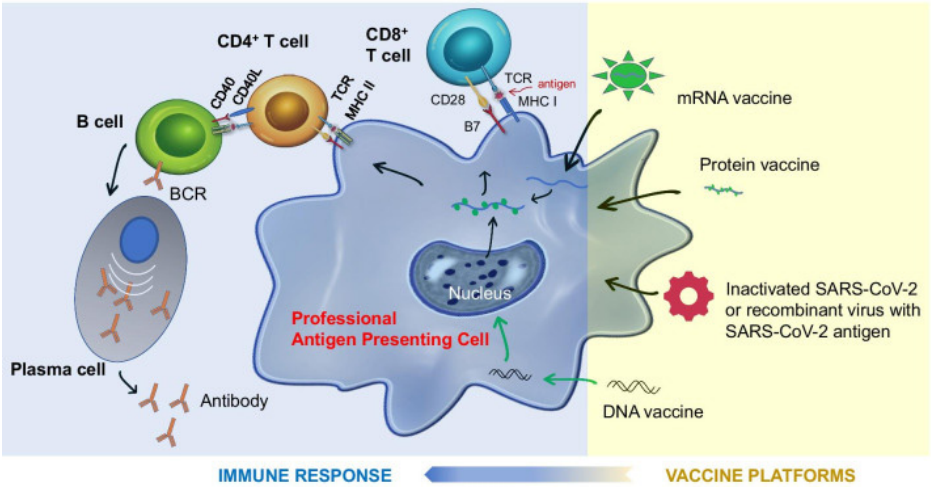

Figure 1 Different platforms of COVID-19 vaccines and mechanisms of antigen presentation, and protective immunity generation.

Table 1 Demonstrating advantages and disadvantages of various COVID-19 vaccine platforms

Vaccine Platform	COVID-19 Vaccines (approved/ in development)	Advantages	Disadvantages
Inactivated Virus	SinoVac (CoronaVac + aluminum)	Prior experience and technology, e.g., quadrivalent influenza vaccine	Poor inducers of CD8+ T-cell immunity
	Sinopharm (Inactivated whole virus SARS-CoV-2 + aluminum)	Easier storage, does not need to be frozen	Need adjuvants to boost
		Entire virus, with all antigens presented	Large batches of live virus pose biosecurity risk
mRNA	Pfizer/BioNTech (BNT162b2)	Unable to integrate into host genome	Frozen for vaccine storage
		Delivery into host cytoplasm	Needs delivery of lipid nanoparticle
		Avoids introducing pathogen (SARS-CoV-2)	
		Avoids anti-vector immunity	
		Easier mass-production	
		Elicit strong humoral and cellular immunity	
DNA	Inovio (INO-4800)	Avois introducing pathogen (SARS-CoV-2)	Delivery into nucleus of host cell
		Easier mass-production	
		Mimics natural infection	
		Elicits strong humoral and cellular immunity	
Protein subunits	Novavax (NVX-CoV2373)	Does not introduce pathogen (SARS-CoV-2)	Lower humoral and cellular immunity response
	Vector Institute (EpiVacCorona)	Being able to focus on antigens that generate neutralizing antibodies	Not efficiently presented
			Require adjuvants to boost
			Produced ex vivo may not retain post-translational conformation or modifications
Replication incompetent adenoviral vector	AstraZeneca (ChAdOx1 nCoV-19/ AZD1222)	Mimics natural infection	Lower efficacy if prior anti-vector immunity exists
	Johnson and Johnson (Ad26. COV2.S)	Avoids pathogen (SARS-CoV-2)	Anti-vector immunity may interfere
	CanSino Biologics (Ad5-nCoV)	Elicits humoral and cellular immunity	
	Gamaleya (Sputnik V)	No new viral particles (Defective Replication)	

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Table 2 Demonstrating recently published clinical trials and ongoing clinical trials on mixing COVID-19 vaccination, as of July 11, 2021

Ongoing Clinical Trials				
Site/Number of Participants	Current Status	Type and Clinical Trial Objective	Group and Vaccine Type	Primary and Secondary Outcomes
	(As of July 11, 2021)			
Austria (NCT04907331)/3,000 participants	Ongoing	Randomized, Controlled Trial, phase II; evaluating safety and efficacy of heterologous vaccination with ChAdOx1-S, AZ (Vaxzevria) followed by BNT162b2, Pfizer/BioNTech) (Comirnaty)	Clinical Trial Arm:	Primary Outcomes:
			Prime:	T-cells response to SARS-CoV-2 (COVID-19) Spike Protein Epitopes in both arms; Neutralizing Antibodies in both arms; Vaccine Failures in both arms
			ChAdOx1-S or ChAdOx1 nCoV-19 vaccine, AZ (Vaxzevria);	
			Boost:	
			BNT162b2 vaccine, Pfizer/BioNTech (Comirnaty) 12 weeks apart	
			Control Arm:	
			Homolog Vaccination with Vaxzerria (Prime/Boost) or Comirnaty (Prime/Boost)	
China	Ongoing	Randomized, Paralell-Controlled Clinical Trials; evaluating safety and immunogenicity of sequential immunization of a recombinant SARS-CoV-2 (COVID-19) vaccine (Adenovirus Type V Vector)	Clinical Trial Arm:	Primary Outcomes:
(NCT04892459)/300 participants			Prime:	Adverse Reactions within 28 days after the booster dose; Genomic Mean Titer (GMT) of Neutralizing Antibodies against Live SARS-CoV-2 (COVID-19) Virus on Day 14 after Booster Dose
			Inactive SARS-CoV-2 (COVID-19) (Vero cell) (Sinovac Research & Development Co., Ltd);	
			Boost:	
			Recombinant SARS-CoV-2 (COVID-19) Ad5 Vectored Vaccine (CanSino Biologics);	
			Comparator Arm: Homogeneous Boost Arm with Inactive Vaccine	
France (NCT04900467)/400 participants	Ongoing	Randomized, Open Label, Non-Inferiority Clinical Trial	Arm 1:	Primary Outcomes:
			Prime: Pfizer/BioNTech mRNA Vaccine;	Anti-Spike IgG Titer 28 Days following Vaccination in both arms
				Secondary Outcomes:
			Boost: Moderna mRNA Vaccine versus Prime: Pfizer/BioNTech mRNA Vaccine;	Adverse Events
			Boost:	

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Table Continued...

Ongoing Clinical Trials				
			Pfizer/BioNTech mRNA Vaccine Arm 2: Prime: Moderna mRNA Vaccine; Boost: Pfizer/BioNTech mRNA Vaccine versus Prime: Moderna mRNA Vaccine; Boost: Moderna mRNA Vaccine	
Canada (MOSAIC) (NCT04894435)/1,300 participants	Ongoing	Randomized Clinical Trial; evaluating the immune response and safety of two different vaccines for the first and second doses and differing between the first and second doses of the two-dose vaccines	Multiple Groups (13) comparing Various Combination of Moderna mRNA vaccine and ChAdOx1 nCOV-19 (AstraZeneca) vaccine in homologous and heterologous prime-boost regimens	Primary Outcomes: Antibody Response to SARS-CoV-2 (COVID-19) Spike Protein at 28 Days following Second Dose of Vaccine; Secondary Outcomes: Pseudo neutralization Assay, T-Cell Testing, Antibody-Dependent Cellular Cytotoxicity (ADCC), Antibody Avidity; Description of Safety Outcomes Over 12 months post-vaccination including serious adverse events (SAEs); Incidence of Grade III solicited local and systemic adverse events, SAEs, AEFIs, within 7 days after vaccination; Durability of Antibody Response to SARS-CoV-2 (COVID-19) Spike Protein over 12 months
USA (National Institute of Health (NIH) Trial) (NCT04889209)/400 participants	Ongoing	Phase I/II, Open-Label Clinical Trial; evaluating safety, reactogenicity and mmunogenicity of a delayed (> 12 weeks) vaccine boost	Vaccines: Ad26.COV2.S (Janssen Pharmaceuticals/Johnson & Johnson), BNT162b2 (Pfizer/BioNTech), or mRNA-1273 (ModernaTX); Boost: Booster shot following complete vaccination will be provided in various combinations via multiple arms of the clinical trial	Primary Outcomes: Response Rate of SARS-CoV-2 (COVID-19) Specific Antibody Binding and Neutralization Titers; Occurrence of SAEs after Last Dose on the clinical Trial and after Delayed Booster Vaccination; Magnitude of SARS-CoV-2 (COVID-19) Specific Antibody Binding and Neutralization Titer
Published Clinical Trials				
Site/Authors/Clinical Trial Name/Number of Participants	Type of Clinical Trial	Group and Vaccine Type	Clinical Trial Outcomes	Adverse Events

Table Continued...

Ongoing Clinical Trials				
Germany/GroB et	Prospective, Observational Clinical Trial	First Dose:	CD4+ and CD8+ T Cells Reacts to SARS-CoV-2 (COVID-19) Spike Peptide Stimulus 2 Weeks Post-Full Vaccination; Neutralizing Activity Against Prevalent Strain B.1.1.7 (Alpha Strain) with Hetrologous Prime Boost was 3.9 times higher than in persons receiving Homologous BNT162b2 vaccination (Pfizer/BioNtech); Strong Neutralization Titers 2 Weeks Post-BNT162b2 vaccine (Pfizer/BioNTech) boost	Prime Dose:
al/26 participants		ChAdOx1 nCoV-19 vaccine (AstraZeneca)		Mild to Moderate Reaction (88.4 %)
		Second Dose:		Boost Dose:
		BNT162b2 vaccine (Pfizer/BioNTech) following 8-week interval		Mild or Moderate Symptom (80.8 %)
		No Control Group		Common Symptoms:
				Pain at the injection site, Fever, Headache, Chills, Myalgia, Fatigue
Germany/Hillus et al/340 participants	Prospective, Observational Cohort Study	Trial Arm 1:	T-cell Reactivity: Significantly higher following Heterologous ChAdOx1/BNT162b2 boost compared to Homologous BNT162b2/BNT162b2 boost; S1-IgG Avidity: High following Heterologous ChAdOx1/ BNT162b2 boost compared to Homologous BNT162b2/ BNT162b2 boost; Neutralizing Antibody Response 3 weeks Post-boost immunization: Homologous BNT162b2 (99.01 %), Heterologous ChAdOx1/ BNT162b2 boost (100.0 %); Serum Antibody Response: Strongly Increased following both Homologous and Heterologous boost	Local eaction: Slight higher frequency following Heterologous ChAdOx1/ BNT162b2 booster compared to Homologous BNT162b2/BNT162b2 booster
		Prime:		Systemic Reactions: Most frequent following prime immunization with ChAdOx1 (86 %) and less frequent following Homologous BNT162b2/ BNT162b2 (65 %) or Heterologous ChAdOx1/BNT162b2 booster vaccination (48 %);
		ChAdOx1 nCoV-19 vacccine (AstraZeneca);		No potential life-threatening reactions following any of the COVID-19 vaccine regimens
		Boost:		
		BNT162b2 vaccine (Pfizer/BioNTech 10-12 weeks apart		
		Trial Arm 2:		
		Homologous BNT162b2 vaccine (Pfizer/BioNTech) (prime and boost) 3 weeks apart		
Spain/Borobia et al/663 participants	Randomized, Phase II Trial	Trial Arm:	Trial Arm:	Similar in both groups:
		Prime: ChAdOx1 nCoV-19 vaccine (Vaxzevria, AstraZeneca);	Greater Immune Response: 150 times antibody 14 Days following Second Dose; 4 times increase in Cellular Immune Response; Effective in Protecting Against SARS-CoV-2 (COVID-19)	Mild (68.3 %); Moderate (29.9 %)

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Table Continued...

Ongoing Clinical Trials				
		Boost:	Control Arm:	Most Common: Headache (44 %); Malaise (41 %); Chills (25 %); Mild Nausea (11 %); Mild Cough (7 %); and Fever (2.5 %)
		BNT162b2 vaccine (Comirnaty, Pfizer/ BioNTech)	Antibody Titers at 14 Days similar to Baseline Titers	
		Control Arm:		
		Received only one dose and not received any second dose of vaccine		
UK/Shaw et al/830 participants	Single-Blind, Randomized, Phase II Trial	Trial Arm 1:	Not yet reported	Greater Systemic Ractogenicity in Heterologous prime-boost regimen than their Homologous counterparts;
		Prime:		Most common symptom: Feverishness
		ChAdOx1 nCoV-19 vaccine (Vaxzevria, AstraZeneca);		No hospitalization
		Boost:		Most of increased Reactogenicity identified within 48 hours following immunization
		BNT162b2 vaccine (Comirnaty, Pfizer/BioNTech)		
		Trial Arm 2:		
		Prime:		
		BNT162b2 vaccine (Pfizer/BioNTech);		
		Boost:		
		ChAdOx1 nCoV-19 vaccine (AstraZeneca)		
		Control Arm:		
		Homologous Schedule:		
		Arm 1:		
		Prime and boost:		
		BNT162b2 vaccine (Pfizer/BioNTech);		
		Arm 2:		
		Prime and boost: ChAdOx1 nCoV-19 vaccine (AstraZeneca)		

Conclusion

It is better to give a different COVID-19 vaccine or mixing and matching COVID-19 vaccination than not administer the second dose at all.

Authors 'contributions

Dr. Attapon Cheepsattayakorn conducted the study framework and wrote the manuscript. Associate Professor Dr. Ruangrong Cheepsattayakorn and Dr. Thanom Jewsuebpong contributed to scientific content and assistance in manuscript writing. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no actual or potential competing financial interests.

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