

***LITERATURE REVIEW: STATUS PERKEMBANGAN
PEMBUATAN VAKSIN SEVERE ACUTE RESPIRATORY
SYNDROME CORONAVIRUS 2 (SARS-CoV-2) DENGAN
PLATFORM INACTIVATED VIRUS***

SKRIPSI

NANI ERNACI

A181027



**SEKOLAH TINGGI FARMASI INDONESIA
YAYASAN HAZANAH
BANDUNG
2022**

***LITERATURE REVIEW: STATUS PERKEMBANGAN
PEMBUATAN VAKSIN SEVERE ACUTE RESPIRATORY
SYNDROME CORONAVIRUS 2 (SARS-CoV-2) DENGAN
PLATFORM INACTIVATED VIRUS***

SKRIPSI

Sebagai salah satu syarat untuk memperoleh gelar Sarjana Farmasi

NANI ERNACI

A181027



**SEKOLAH TINGGI FARMASI INDONESIA
YAYASAN HAZANAH
BANDUNG
2022**

**LITERATURE REVIEW: STATUS PERKEMBANGAN PEMBUATAN
VAKSIN SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2
(SARS-CoV-2) DENGAN PLATFORM INACTIVATED VIRUS**

NANI ERNACI

A181027

Juli 2022

Disetujui Oleh:

Pembimbing



Dr. Erman Tritama, M.Si

Pembimbing



Nur Asni Setiani, M.Si

Kutipan atau saduran baik sebagian ataupun seluruh naskah, harus menyebut nama pengarang dan sumber aslinya, yaitu Sekolah Tinggi Farmasi Indonesia

Skripsi ini dipersembahkan untuk aku, Terimakasih kepada Allah SWT, Keluarga ku Mama, Mimi, Oduts (Dzaky), serta orang-orang baik yang sudah memberikan doa dan semangat untuk menyelesaikan skripsi ini.

ABSTRAK

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) adalah virus yang menyerang sistem pernapasan sehingga menyebabkan terjadinya *Coronavirus disease 2019* (COVID-19). *Inactivated virus* adalah salah satu *platform* yang digunakan untuk pengembangan vaksin SARS-CoV-2. Tujuan penelitian ini untuk memberikan informasi mengenai perkembangan vaksin SARS-CoV-2 yang menggunakan platform *Inactivated virus*, dan memberikan informasi cara pembuatan (*drugs substance* dan *drugs product*) dan efektifitas jenis vaksin ini. Metode penelitian dalam artikel review ini menggunakan penelusuran dengan database *PubMed*, dan *Google Scholar*. Hasil penelitian didapatkan informasi perkembangan vaksin SARS-CoV-2 dengan platform *inactivated virus* beberapa vaksin yang sedang dilakukan uji klinis fase 4, vaksin tersebut diantaranya vaksin CoronaVac, *Inactivated SARS-CoV-2 vaccine (Vero cell)* dan BBIBP-CorV. Berdasarkan hasil uji klinik vaksin dengan platform ini menghasilkan tingkat efikasi >50%. Vaksin CoronaVac efektif melawan virus SARS-CoV-2 varian gamma, Delta dan Omicron dengan efektivitas 46,8%, 59%, dan 38,2%. *Drugs substance* dibuat dengan memformulasikan *strain* virus SARS-CoV-2 yang diinaktivasi dengan β -propiolakton atau dengan formaldehid dan diberikan tambahan Aluminium hidroksida, Algel, atau CpG 108 sebagai adjuvant.

Kata Kunci: SARS-CoV-2, Vaksin, *Inactivated Platform*, Uji Praklinik, Uji Klinik, Efikasi, Efektivitas

ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a virus that attacks the respiratory system, causing Coronavirus disease 2019 (Covid-19). Inactivated virus is one of the platforms used to develop the SARS-CoV-2 vaccine. This research aimed to inform about the SARS-CoV-2 vaccine development using inactivated virus platform and to provide information on how to produce (drug substance and drug product) and the effectiveness of this type of vaccine. This article review applied a search using the PubMed database and Google Scholar as the research method. The results of the study obtained information on the development of the SARS-CoV-2 vaccine by an inactivated virus platform for several vaccines currently undergoing phase 4 clinical trials, the vaccines include the CoronaVac vaccine, Inactivated SARS-CoV-2 vaccine (Vero cell) and BBIBP-CorV. Based on the results of clinical trials of vaccines with this platform, the efficacy rate was >50%. The CoronaVac vaccine was effective against the SARS-CoV-2 variants of gamma, Delta and Omicron with 46.8%, 59%, and 38.2% effectiveness. The drug's substance was prepared by formulating the SARS-CoV-2 virus strain which is inactivated with β -propiolactone or formaldehyde and added with Aluminum hydroxide, Algal, or CpG 108 as an adjuvant.

Keywords: SARS-CoV-2, Vaccine, Inactivated Platform, Praclinical Trial, Clinical Trial, Efficacy, Effectiveness

KATA PENGANTAR

Bismillahirrahmanirrahim,

Puji dan syukur penulis panjatkan ke hadirat Allah SWT atas segala berkah rahmat dan ridho-Nya penulis dapat menyelesaikan penelitian dan penulisan skripsi yang berjudul “***Literature Review: Status Perkembangan Vaksin Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Dengan Platform Inactivated Virus***”. Penelitian dan penulisan skripsi ini dilakukan untuk memenuhi salah satu syarat untuk mendapatkan gelar sarjana pada jurusan Farmasi Sekolah Tinggi Farmasi Indonesia. Penulis mengucapkan terima kasih kepada dosen pembimbing Dr. Erman Tritama, M.Si dan Nur Asni Setiani, M.Si atas bimbingan, nasihat, serta dukungan yang diberikan. Pada kesempatan ini, tidak lupa penulis mengucapkan terima kasih yang sebesar – besarnya kepada :

1. Dr. apt. Adang Firmansyah, M.Si selaku Ketua Sekolah Tinggi Farmasi Indonesia,
2. Dr. Diki Prayugo Wibawa, M.Si selaku Wakil Ketua I Sekolah Tinggi Farmasi Indonesia,
3. Dr. apt. Wiwin Winingsih , M.Si selaku Kepala Program Studi,
4. Prof. Dr. apt. Aang Hanafiah WS selaku Dosen Wali yang telah banyak memberikan bimbingan dan arahan kepada penulis,
5. Seluruh staf dosen, staf administrasi serta karyawan Sekolah Tinggi Farmasi Indonesia,
6. Serta teman – teman angkatan 2018 yang telah memberikan inspirasi dan kegembiraan selama penulis kuliah di Sekolah Tinggi Farmasi Indonesia.

Oleh karena itu, diharapkan masukan berupa kritik dan saran yang bersifat membangun untuk perbaikan di masa yang akan datang. Penulis berharap semoga tugas akhir ini akan memberikan manfaat bagi penulis sendiri dan juga bagi pihak lain yang berkepentingan.

Bandung, Juli 2022

Penulis

DAFTAR ISI

LEMBAR PENGESAHAN.....	i
ABSTRAK.....	iv
ABSTRACT.....	v
KATA PENGANTAR.....	vii
DAFTAR TABEL	ix
DAFTAR GAMBAR.....	x
DAFTAR LAMPIRAN.....	xi
BAB I PENDAHULUAN.....	1
1.1 Latar Belakang.....	1
1.2 Identifikasi Masalah	3
1.3 Tujuan Penelitian.....	3
1.4 Kegunaan Penelitian.....	3
1.5 Luaran Penelitian.....	4
1.6 Waktu dan Tempat Penelitian	4
BAB II TINJAUAN PUSTAKA.....	5
2.1 Severe Acute Respiratory Syndrome Corona 2 (SARS-CoV2)	5
2.2 Patogenesis	6
2.3 Vaksin.....	7
2.4 Mekanisme Kerja Vaksin	8
2.5 Platform Pembuatan Vaksin	10
2.5.1 <i>Inactivated Virus Vaccine</i>	10
2.5.2 <i>Live Attenuated-Virus (LAV) Vaccine</i>	11

2.5.3	<i>Protein Subunit Vaccine</i>	12
2.5.4	<i>Virus Like Particle Vaccine</i>	12
2.5.5	<i>Viral Vector Vaccine</i>	12
2.5.6	<i>DNA Vaccine</i>	13
2.5.7	<i>RNA Vaccine</i>	13
2.6	Tahap Pembuatan Vaksin	14
BAB III METODE PENELITIAN		17
3.1	Desain Penelitian	17
3.2	Metode Pengumpulan Data	17
3.3	Kriteria Inklusi dan Eksklusi	18
3.3.1	Kriteria Inklusi	18
3.3.2	Kriteria Eksklusi	18
3.4	Metode Analisis Data	18
3.5	Publikasi	18
BAB IV HASIL PENELITIAN DAN PEMBAHASAN.....		20
4.1	Uji Praklinik	20
4.2	Uji Klinik.....	27
4.3	Efektivitas Vaksin	36
BAB V KESIMPULAN DAN ALUR PENELITIAN SELANJUTNYA		40
5.1	Kesimpulan.....	40
5.2	Alur Penelitian Selanjutnya.....	40
DAFTAR PUSTAKA		41
LAMPIRAN.....		50

DAFTAR TABEL

Tabel	Halaman
4.1 Hasil Uji Praklinik	20
4.2 Hasil Uji Klinik.....	28
4.3 Efektivitas Vaksin Inactivated SARS-CoV-2.....	37

DAFTAR GAMBAR

Gambar	Halaman
2.1 Struktur SARS-CoV-2	5
2.2 Mekanisme Kerja Vaksin.....	9
2.3 Hasil Pengumpulan Data.....	19

DAFTAR LAMPIRAN

Lampiran	Halaman
1. Jurnal	500

DAFTAR PUSTAKA

- Abdoli, A., Aalizadeh, R., Aminianfar, H., Kianmehr, Z., Teimoori, A., Azimi, E., Emamipour, N., Eghtedardoost, M., Siavashi, V., Jamshidi, H., Hosseinpour, M., Taqavian, M., Jalili, H. 2022. "Safety and Potency of BIV1-CovIran Inactivated Vaccine Candidate for SARS-CoV-2: A Preclinical Study". *Rev Med Virol* 32(3):e2305.
- Al Kaabi, N., Oulhaj, A., Ganesan, S., Al Hosani, F.I., Najim, O., Ibrahim, H., Acuna, J., Alsuwaidi, A. R., Kamour, A. M., Alzaabi, A., Al Shehhi, B. A., Al Safar, H., Hussein, S. E., Abdalla, J. S., Al Mansoori, D. S. N., Al Hammadi, A. A. K., Amari, M. A., Al Romaithi, A. K., Weber, S., Elavalli, S., Eltantawy, I., Alghaithi, N. K., Al Azazi, J. N., Holt, S. G., Mostafa, M., Halwani, R., Khalak, H., Elamin, W., Beiram, R., Zaher, W. 2022. "Effectiveness of BBIBP-CorV Vaccine Against Severe Outcomes of COVID-19 in Abu Dhabi, United Arab Emirates". *Nat Commun* 13(1):3215.
- Al-Jighefee, Hadeel, T., Hoda, Najjar., Muna, N. Ahmed., Abeer, Qush., Sara, Awwad., and Layla, Kamareddine. 2021. "COVID-19 Vaccine Platforms: Challenges and Safety Contemplations" *Vaccines* 9 (10): 1196.
- Astuti I, and Ysrafil. 2020. "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response". *Diabetes Metab Syndr* 14:407–412.
- Attia Y. A., El-Saadony, M. T., Swelum, A. A, Qattan, S. Y. A., Al-Qurashi, A. D., Asiry, K. A., Shafi, M. E., Elbestawy, A. R., Gado, A. R., Khafaga, A. F., Hussein, E. O. S., Ba-Awad, H., Tiwari, R., Dhama, K., Alhussaini, B., Alyileili, S. R., El-Tarabily, KA., and Abd El-Hack M. E. 2021. "COVID-19: Pathogenesis, Advances in Treatment and Vaccine Development and Environmental Impact-an Updated Review". *Environ Sci Pollut Res Int* 28(18): 22241-22264.
- BioRender. 2022. "Human Coronavirus". Retrieved December 31, 2021 (<https://app.biorender.com/biorendertemplates/figures/5e99f5395fd61e0028682c01/t-5f21e90283765600b08fbe9d-human-coronavirus-structure>).
- Cascella, M., Rajnik, M., Aleem, A., Dulebohn, S. C., and Di Napoli, R. 2021. *Features, Evaluation, and Treatment of Coronavirus (COVID-19)*. *StatPearls*.
- Cerqueira- Silva, T., Oliveira, V. D. A, Pescarini, J.M., Júnior J. B., Machado, T. M., Flores-Ortiz, R., Penna, G. O., Ichihara, M. Y., de Barros, J. V., Barreto, M. L., Werneck, G. L., Barral-Netto, M. 202. "Influence of age on the

effectiveness and duration of protection in Vaxzevria and CoronaVac vaccines”. *medRxiv* 6: 100154.

Che, Y., Liu, X., Pu, Y., Zhou, M., Zhao, Z., Jiang, R., Yin, Z., Xu, M., Yin, Q., Wang, J., Pu, J., Zhao, H., Zhang, Y., Wang, L., Jiang, Y., Lei, J., Zheng, Y., Liao, Y., Long, R., Yu, L., Cui, P., Yang, H., Zhang, Y., Li, J., Chen, W., He, Z., Ma, K., Hong, C., Li, D., Jiang, G., Liu, D., Xu, X., Fan, S., Cheng, C., Zhao, H., Yang, J., Li, Y., Zou, Y., Zhu, Y., Zhou, Y., Guo, Y., Yang, T., Chen, H., Xie, Z., Li, C., and Li, Q. 2021. “Randomized, Double-Blinded, Placebo-Controlled Phase 2 Trial of an Inactivated Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine in Healthy Adults”. *Clin Infect Dis* 73(11):e3949-e3955.

Depkes RI. 2020. *Farmakope Indonesia*. Edisi VI. Departemen Kesehatan Republik Indonesia. Jakarta. Hal 64.

Devashish, D., Adil, R. Khan., Manish, S., Ankit M., Shivdas N., Parul K., Ayan M., Ganesh T. Maher., Rohit, K., Ayush A., Naveen R. Gowda., Vikas H., Parmeshwar K., Shivam P., Pandey, Arvind, K., Animesh, R., Pankaj, J., Neeraj, N., Aashish, C., Megha, B., Karan, M., Rakesh, L., Sanjeev, S., Lalit, D., Naveet, W., and Randeep, G. 2022. “Effectiveness of an inactivated virus-based SARS-CoV-2 vaccine, BBV152, in India: a test-negative, case-control study”. *The Lancet Infectious Diseases* 22 (3): 349-356

Dhama, K., Patel, S. K., Pathak, M., Yattoo, M. I., Tiwari, R., Malik, Y. S., Singh R., Sah, R., Rabaan, A. A., Bonilla-Aldana, D. K., and Rodriguez-Morales, A. J. 2020. “An update on SARS-CoV-2/ COVID-19 with particular reference to its clinical pathology, pathogenesis, immunopathology and mitigation strategies”. *Travel Med Infect Dis* 37:1-10.

Duc, Dang A., Dinh, Vu T., Hai, Vu H., Thanh, Ta V., Thi, Van Pham A., Thi, Ngoc Dang M., Van, Le B., Huu, Duong T., Van, Nguyen D., Lawpoolsri, S., Chinwangso, P., McLellan, J. S., Hsieh, C. L., Garcia-Sastre, A., Palese, P., Sun, W., Martinez, J. L., Gonzalez-Dominguez, I., Slamang, S., Manuel, Carreño J., Tcheou, J., Krammer, F., Raskin, A., Minh, Vu H., Cong, Tran T., Mai, Nguyen H., Mercer, L. D., Raghunandan, R., Lal, M., White, J. A., Hjorth, R., Innis, B. L., and Scharf, R. 2022. “Safety and immunogenicity of an egg-based inactivated Newcastle disease virus vaccine expressing SARS-CoV-2 spike: Interim results of a randomized, placebo-controlled, phase 1/2 trial in Vietnam”. *Vaccine* 40(26):3621-3632.

Ella, R., Reddy, S., Blackwelder, W., Potdar, V., Yadav, P., Sarangi, V., Aileni, V. K., Kanungo, S., Rai, S., Reddy, P., Verma, S., Singh, C., Redkar, S., Mohapatra, S., Pandey, A., Ranganadin, P., Gumashta, R., Multani, M., Mohammad, S., Bhatt, P., Kumari, L., Sapkal, G., Gupta, N., Abraham, P.,

- Panda, S., Prasad, S., Bhargava, B., Ella, K., and Vadrevu, K. M. 2021. "COVAXIN Study Group. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial". *Lancet* 398(10317):2173-2184.
- Ella, R., Reddy, S., Jogdand, H., Sarangi, V., Ganneru, B., Prasad, S., Das, D., Raju, D., Praturi, U., Sapkal, G., Yadav, P., Reddy, P., Verma, S., Singh, C., Redkar, S. V., Gillurkar, C. S., Kushwaha, J. S., Mohapatra, S., Bhate, A., Rai, S., Panda, S., Abraham, P., Gupta, N., Ella, K., Bhargava, B., and Vadrevu K. M. 2021. "Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial". *Lancet Infect Dis* 21(7):950-961.
- Fadlyana, E., Rusmil, K., Tarigan, R., Rahmadi, A. R., Prodjosoewojo, S., Sofiatin, Y., Khrisna, C. V., Sari, R. M., Setyaningsih, L., Surachman, F., Bachtiar, N. S., Sukandar, H., Megantara, I., Murad, C., Pangesti, K. N. A., Setiawaty, V., Sudigdoadi, S., Hu, Y., Gao, Q., and Kartasasmita, C. B. 2021. "A phase III, observer-blind, randomized, placebo-controlled study of the efficacy, safety, and immunogenicity of SARS-CoV-2 inactivated vaccine in healthy adults aged 18-59 years: An interim analysis in Indonesia". *Vaccine* 39(44): 6520-6528.
- Food and Drug Administration (FDA) .1999. *Guidance for Industry Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product*. 1-34. Retrieved January 20, 2022 (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-and-format-chemistry-manufacturing-and-controls-information-and-establishment-description-1>).
- Gao, Q., Bao, L., Mao, H., Wang, L., Xu, K., Yang, M., Yajing, Li., Ling, Z., Nan, W., Zhe, L., Hong, G., Xiaoqin, Ge., Biao, K., Yaling, Hu., Jiangning, Liu., Fang, Cai., Deyu, Jiang., Yanhui, Yin., Chengfeng, Qin., Jing, Li., X, Gong., Xiuyu, L., Wen, S., Dongdong, W., Hengming, Z., Lang, Zhu., Wei, D., Yurong, L., Jinxing, L., Changgui, Li., Xiangxi, W., Weidong, Y., Yanjun, Z., and Chuan, Q. 2020. "Development of an inactivated vaccine candidate for SARS-CoV-2". *Science* 369:77– 81.
- Gennaro, F., Di, Pizzol, D., Marotta, C., Antunes, M., Racalbuto, V., Veronese, N., and Smith, L. 2020. "Coronavirus Diseases (COVID-19) Current Status and Future Perspectives : A Narrative Review". *International Environmental* 17(2690): 1-11.

- Ghattas, M., Dwivedi, G., Lavertu, M., and Alameh, M. G. 2021. "Vaccine Technologies and Platforms for Infectious Diseases: Current Progress, Challenges, and Opportunities". *Vaccines (Basel)* 9(12):1490.
- Green, Martin David dan Al-Humadi, Nabil Hussain. 2013. Preclinical Toxicology of Vaccines. 619-645.
- Haley E. Randolph dan Luis B. Barreiro. 2020. "Herd Immunity: Understanding COVID-19". *PubMed*. 52: 737-741.
- Huang, Z., Jiang, Q., Wang, Y., Yang, J., Du, T., Yi, H., Li, C., Li, Y., Wu, Z., Fan, S., Liao, Y., Zhang, Y., Wang, L., Jiang, G., Tang, D., Ye, Y., Wang, C., Li, Z., Zhang, C., Ma, K., and Li, Q. 2021. "SARS-CoV-2 inactivated vaccine (Vero cells) shows good safety in repeated administration toxicity test of Sprague Dawley rats". *Food Chem Toxicol* 152:112239.
- Jara, A., Undurraga, E. A., González, C., Paredes, F., Fontecilla, T., Jara, G., Pizarro, A., Acevedo, J., Leo, K., Leon, F., Sans, C., Leighton, P., Suárez, P., García-Escorza, H., and Araos, R. 2021. "Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile". *N Engl J Med* 385(10):875-884.
- Jara, A., Undurraga, E. A., Zubizarreta, J. R., González, C., Acevedo, J., Pizarro, A., Vergara, V., Soto-Marchant, M., Gilabert, R., Flores, J. C., Suárez, P., Leighton, P., Eguiguren, P., Ríos, J. C., Fernandez, J., García-Escorza, H., and Araos R. 2022. "Effectiveness of CoronaVac in children 3-5 years of age during the SARS-CoV-2 Omicron outbreak in Chile". *Nature Medicine* 8: 1377-1380.
- Jara, A., Undurraga, E. A., Zubizarreta J. R, González, C., Pizarro, A., Acevedo, J., Leo, K., Paredes, F., Bralic, T., Vergara, V., Mosso, M., Leon, F., Parot, I., Leighton, P., Suárez, P., Rios, J. C., García-Escorza, H., and Araos, R. 2022. "Effectiveness of homologous and heterologous booster doses for an inactivated SARS-CoV-2 vaccine: a large-scale prospective cohort study". *Lancet Glob Health* 10: e798-806.
- Jiang, S., Hillyer, C., and Du, L. 2020. *Neutralizing antibodies against SARS-CoV-2 and other human Coronaviruses. Trends Immunol* 41(5): 355-359.
- Kayne, S. B. and Jepson, M. H. 2004. *Veterinary Pharmacy*. London: The Pharmaceutical Press.
- Khairullin, B., Zakarya, K., Orynbayev, M., Abduraimov, Y., Kassenov, M., Sarsenbayeva, G., Sultankulova, K., Chervyakova, O., Myrzakhmetova, B., Nakhanov, A., Nurpeisova, A., Zhugunissov, K., Assanzhanova, N.,

- Nurabayev, S., Kerimbayev, A., Yershebulov, Z., Burashev, Y., Kulmagambetov, I., Davlyatshin, T., Sergeeva, M., Buzitskaya, Z., Stukova, M., and Kutumbetov L. 2022. “Efficacy and safety of an inactivated whole-virion vaccine against COVID-19, QazCovid-in®, in healthy adults: A multicentre, randomised, single-blind, placebo-controlled phase 3 clinical trial with a 6-month follow-up”. *EClinicalMedicine* 50:101526.
- Kuo, T. Y., Lin, M. Y., Coffman, R. L., Campbell, J. D., Traquina, P., Lin, Y. J., Liu, L. T., Cheng, J., Wu, Y. C., Wu, C. C., Tang, W. H., Huang, C. G., Tsao, K. C., and Chen, C. 2020. “Development of CpG-adjuvanted stable prefusion SARS-CoV-2 spike antigen as a subunit vaccine against COVID-19”. *Sci Rep* 10(1):20085.
- Lazarus, R., Christian, Taucher., Claire, Brown., Irena, Corbic., Leon, Danon., Katrin, Dubischar., Christopher, J. A. Duncan., Susanne, Eder-Lingelbach., Saul, N. Faust., Christopher, Green., Karishma, Gokani., Romana, Hochreiter., Johanna, K. Wright., Dowan, Kwon., Alexander, Middleditch., Alasdair, P. S. Munro., Kush, Naker., Florentina, P. D. Price., Benedicte, Querton., Tawassal, Riaz., Amy, Ross-Russell., Amada, Sanchez-Gonzalez., Hayley, Wardle., Sarah, Warren., Adam, Finn and the Valneva Phase 1 Trial Group. 2021. “Immunogenicity and safety of inactivated whole virion Coronavirus vaccine with CpG (VLA2001) in healthy adults aged 18 to 55: a randomised phase 1 /2 clinical trial”. *MedRxiv* 1-30.
- Li X. N., Huang, Y., Wang W, Jing, Q. L., Zhang, C. H., Qin, P. Z., Guan, W. J., Gan, L., Li, Y. L, Liu, W. H., Dong, H., Miao, Y. T., Fan, S. J., Zhang, Z. B., Zhang, D. M, and Zhong, N. S. *Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study*. *Emerg Microbes Infect* 10(1):1751-1759.
- Li, Y. H., Hu, C. Y., Wu, N. P., Yao, H. P., and Li L. J. 2019. “Molecular Characteristics, Functions, and Related Pathogenicity of MERS-CoV Proteins”. *Engineering (Beijing)* 5: 940–947.
- Medeiros-Ribeiro, A.C., Nadia E. Aikawa, Carla G. S. Saad, Emily F. N. Yuki, Tatiana Pedrosa, Solange R. G. Fusco, Priscila T. Rojo, Rosa M. R. Pereira, Samuel K. Shinjo, Danieli C. O. Andrade, Percival D. Sampaio-Barros, Carolina T. Ribeiro, Giordano B. H. Deveza, Victor A. O. Martins, Clovis A. Silva, Marta H. Lopes, Alberto J. S. Duarte, Leila Antonangelo, Ester C. Sabino, Esper G. Kallas, Sandra G. Pasoto and Eloisa Bonfa. 2021. “Immunogenicity And Safety of The CoronaVac Inactivated Vaccine in Patients With Autoimmune Rheumatic Diseases: A Phase 4 Trial”. *Nat Med* 27: 1744–1751.

- Mohraz, M., Salehi, M., Tabarsi, P., Abbasi-Kangevari M, Ghamari SH, Ghasemi E, Amini Pouya M, Rezaei N, Ahmadi N, Heidari K, Malekpour MR, Nasiri M, Amirzargar AA, Saeedi Moghaddam S, Larijani B., and Hosseini, H. 2022. “Safety and immunogenicity of an inactivated virus particle vaccine for SARS-CoV-2, BIV1-CovIran: findings from double-blind, randomised, placebo-controlled, phase I and II clinical trials among healthy adults”. *BMJ* 12(4):e056872.
- Mousavizadeh L, Ghasemi S. 2020. “Genotype and Phenotype of COVID-19: Their Roles in pathogenesis”. *J Microbiol Immunol Infect* 54(2): 159-162.
- Muhammad, Adnan Shareen., Sulaiman, Khan., Abeer, Kazmi., Nadia, Bashir., and Rabea, Siddique. 2020. “COVID-19 Infection: Origin, Transmission, And Characteristic of Human Coronaviruses”. *Science direct* 24: 91-98.
- Ophinni, Y., Hasibuan, A. S., Widhani, A., Maria, S., Koesnoe, S., Yuniastuti, E., Karjadi, T. H., Rengganis, I., and Djauzi, S. 2020. “COVID-19 Vaccines: Current Status and Implication for Use in Indonesia”. *Acta Med Indones* 52(4):388-412.
- Palacios, R., Batista, A. P., Albuquerque, C. S. N., Patiño, E. G., Sabtos, J., Conde, M., Piorelli, R., Junior, L., Raboni, S., Ramos, F., Romero, G., Leal, F., Camargo, L., Aoki, F., Coelho, E., Oliveira, D., Fontes, C., Pileggi, G., iqueira, A., Oliveira, D., Botosso, V., Zeng, G., Xin, Q., Teixeira, M., Nogueira, M., and Kallas, E. 2021. “Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: The PROFISCOV study”. *SSRN* P. 1-66
- Pavel, S. T. I., Yetiskin, H., Uygut, M. A., Aslan, A. F., Aydın, G., İnan, Ö., Kaplan, B., and Ozdarendeli, A. 2021.”Development of an Inactivated Vaccine against SARS CoV-2”. *Vaccines* 9(11):1266.
- Pollard, A. J., and Bijker, E. M. 2021. “A Guide to Vaccinology: from Basic Principles To New Developments”. *Nat Rev Immunol* 21: 83–100.
- Promptchara, E., Ketloy, C., and Palaga, T. 2020. “Immune Responses in COVID-19 and Potential Vaccines: Lessons Learned From SARS and MERS Epidemic”. *Asian Pac J Allergy Immunol* 38(1):1–9.
- Pu, J., Yu, Q., Yin, Z., Zhang, Y., Li, X., Yin, Q., Chen, H., Long, R., Zhao, Z., Mou, T., Zhao, H., Feng, S., Xie, Z., Wang, L., He, Z., Liao, Y., Fan, S., Jiang, R., Wang, J., Zhang, L., Li, J., Zheng, H., Cui, P., Jiang, G., Guo, L., Xu, M., Yang, H., Lu, S., Wang, X., Gao, Y., Xu, X., Cai, L., Zhou, J., Yu, L., Chen, Z., Hong, C., Du, D., Zhao, H., Li, Y., Ma, K., Ma, Y., Liu, D., Yao, S., Li, C., Che, Y., Liu, L., and Li, Q. 2021. “The safety and immunogenicity of an

inactivated SARS-CoV-2 vaccine in Chinese adults aged 18-59 years: A phase I randomized, double-blinded, controlled trial”. *Vaccine* 39(20):2746-2754.

- Ranzani, O. T., Hitchings, M. D., Dorion, M., D'Agostini, T. L., de Paula, R. C., de Paula, O. F. P., Villela, E. F. M., Torres, M. S. S., de Oliveira, S. B., Schulz, W., Almiron, M., Said, R., de Oliveira, R. D., Vieira da Silva, P., de Araújo, W. N., Gorinchteyn, J. C., Andrews, J. R., Cummings, D. A. T., Ko, A. I., and Croda, J. 2021. “Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid- 19 in Brazil: test negative case- control study”. *BMJ* 374: 1-12.
- Saborni, Chakraborty., Vamsee, Mallajosyula., Cristina, M. Tato., Gene, S., Tan, Taia., and T. Wang. 2021. “SARS-CoV-2 vaccines in advanced clinical trials: Where do we stand”. *ScienceDirect* 172: 314-338.
- Sa-nguanmoo, N., Namdee, K., and Khongkow, M. *et al.* 2022. “Review: Development of SARS-CoV-2 Immuno-Enhanced COVID-19 Vaccines with Nano-Platform”. *Nano Res.* 15: 2196–2225.
- Sari, Indah Pitaloka., dan Sriwidodo. 2020. “Perkembangan Teknologi Terkini dalam Mempercepat Produksi Vaksin Covid-19”. *Majalah Farmasetika* 5(5): 204-217.
- Sharma, Omna., Sultan, Ali A., Ding, Hong., dan Triggle, Chris R. 2020. “A Review of the Progress and Challenges of Developing a Vaccine for COVID-19”. *Front. Immunol* P. 11: 1-17.
- Sun, W., Liu, Y., Amanat, F., González-Domínguez, I., McCroskery, S., Slamanig, S., Coughlan, L., Rosado, V., Lemus, N., Jangra, S., Rathnasinghe, R., Schotsaert, M., Martinez, J. L., Sano, K., Mena, I., Innis, B. L., Wirachwong, P., Thai, D. H., Oliveira, R. D. N., Scharf, R., Hjorth, R., Raghunandan, R., Krammer, F., García-Sastre, A., and Palese, P. 2021. “A Newcastle disease virus expressing a stabilized spike protein of SARS-CoV-2 induces protective immune responses”. *Nat Commun* 12(1):6197.
- Syaodih, Nana. 2009. *Metode Penelitian Pendidikan*. Bandung: Remaja Rosdakarya. Hal 52.
- Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T, and Velesler D. 2020. “Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein”. *PubMed* 181(2): 282-292.
- Wang, H., Zhang, Y., Huang, B., Quan, Y., Wang, W., Xu, W., Li, N., Zhang, J., Hong., Liang, Y., Bao, L., Xu, Y., Ding, L., Zhou, W., Gao, H., Liu, J., Niu, P., and Yang, X. 2020. “Development of an inactivated vaccine candidate,

- BBIBP-CorV, with potent protection against SARS-CoV-2". *Cell* 182(3):713–721.
- Wang, Ze-Jun., Hua-Jun, Zhang., Jia, Lua., Kang-Wei, Xu., Cheng, Peng., Jing, Guo., Xiao-Xiao, Gao., Xin, Wan., Wen-Hui, Wang., Chao, Shan., Su-Cai, Zhang., Jie, Wu., An-Na, Yang., Yan, Zhu., Ao, Xiao., Lei, Zhangc., Lie, Fu., Hao-Rui, Si., Qian, Cai., Xing-Lou, Yang., Lei, You., Yan-Ping, Zhou., Jing, Liua., De-Qing, Pang., Wei-Ping, Jin., Xiao-Yu, Zhang., Sheng-Li, Meng., Yun-Xia, Sun., Ulrich, Desselberger., Jun-Zhi, Wang., Xin-Guo, Li., Kai, Duana., Chang-Gui, Li., Miao, Xu., Zheng-Li, Shi., Zhi-Ming, Yuan., Xiao-Ming, Yang., and Shuo, Shen. 2020. "Low toxicity and high immunogenicity of an inactivated vaccine candidate against COVID-19 in different animal models". *PubMed* 9: 2607-2618.
- Wenjiang, Fu., Jieni, Li., and Paul. Scheet. 2020. "Covid-19 Vaccine Efficacy: Accuracy, Uncertainty and Projection of Cases". *MedRxiv* 16: 1-6.
- World Health Organization (WHO). 2020. "Update On COVID-19 Vaccine Development". https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update45-vaccines-developement.pdf?sfvrsn=13098bfc_5.
- World Health Organization (WHO). 2021. "Vaccine Efficacy, Effectiveness and protection". Retrieved July 19, 2022 (<https://www.who.int/news-room/feature-stories/detail/vaccine-efficacy-effectiveness-and-protection#:~:text=All%20COVID%2D19%20vaccines%20approved,for%20ongoing%20safety%20and%20effectiveness>)
- World Health Organization (WHO). 2022. "WHO Coronavirus (COVID-19) Dashboard. Retrieved February 23, 2022.
- World Health Organization (WHO). 2022. "COVID-19 vaccine tracker and landscape". Retrieved July, 22 2022 (<https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>)
- Wu, Z., Hu, Y., Xu, M., Chen, Z., Yang, W., Jiang, Z., Li, M., Jin, H., Cui, G., Chen, P., Wang, L., Zhao, G., Ding, Y., Zhao, Y., and Yin, W. 2021. "Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial". *Lancet Infect Dis* 21(6):803-812.

- Xia, S., Duan, K., Zhang, Y., Zhao, D., Zhang, H., Xie, Z., Li, X., Peng, C., Zhang, Y., Zhang, W., Yang, Y., Chen, W., Gao, X., You, W., Wang, X., Wang, Z., Shi, Z., Wang, Y., Yang, X., Zhang, L., Huang, L., Wang, Q., Lu, J., Yang, Y., Guo, J., Zhou, W., Wan, X., Wu, C., Wang, W., Huang, S., Du, J., Meng, Z., Pan, A., Yuan, Z., Shen, S., Guo, W., and Yang, X. 2020. "Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials". *JAMA* 324(10):951-960.
- Xia, S., Zhang, Y., Wang, Y., Wang, H., Yang, Y., Gao, G. F., Tan, W., Wu, G., Xu, M., Lou, Z., Huang, W., Xu, W., Huang, B., Wang, W., Zhang, W., Li, N., Xie, Z., Zhu, X., Ding, L., You, W., Zhao, Y., Zhao, J., Huang, L., Shi, X., Yang, Y., Xu, G., Wang, W., Liu, P., Ma, M., Qiao, Y., Zhao, S., Chai, J., Li, Q., Fu, H., Xu, Y., Zheng, X., Guo, W., and Yang, X. 2022. "Safety and immunogenicity of an inactivated COVID-19 vaccine, BBIBP-CorV, in people younger than 18 years: a randomised, double-blind, controlled, phase 1/2 trial". *Lancet Infect Dis* 22(2):196-208.
- Zahid, Muhammad Nauman; Moosa, Mustafa Shehab; Perna, Simone; and Ebtisam Bin Buti. 2021. "A Review On COVID-19 Vaccines: Stages of Clinical Trials, Mode of Actions and Efficacy". *Arab Journal of Basic and Applied Sciences* 28 (1): 225-233.
- Zakarya, K., Kutumbetov, L., Orynbayev, M., Abduraimov, Y., Sultankulova, K., Kassenov, M., Sarsenbayeva, G., Kulmagambetov, I., Davlyatshin, T., Sergeeva, M., Stukova, M., and Khairullin, B. 2021. "Safety and immunogenicity of a QazCovid-in® inactivated whole-virion vaccine against COVID-19 in healthy adults: A single-centre, randomised, single-blind, placebo-controlled phase 1 and an open-label phase 2 clinical trials with a 6 months follow-up in Kazakhstan". *EClinicalMedicine* 39:101078.
- Zhang, Y., Zeng, G., Pan, H., Li, C., Hu, Y., Chu, K., Han, W., Chen, Z., Tang, R., Yin, W., Chen, X., Hu, Y., Liu, X., Jiang, C., Li, J., Yang, M., Song, Y., Wang, X., Gao, Q., and Zhu, F. 2021. "Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial". *Lancet Infect Dis* 21(2):181-192.
- Zhugunissov, K., Zakarya, K., Khairullin, B., Orynbayev, M., Yergali, A., Kassenov, M., Sultankulova, K., Kerimbayev, A., Sergazy, N., Myrzakhmetova, B., Aziz, N., Ainur, N., Olga, C., Nurika, A., Erbol, B., Muratbay, M., Oldir, A., Syrym, K., Nurlan, K., S, Moldir, T., and Lespek, K. 2021. "Development of the Inactivated QazCovid-in Vaccine: Protective Efficacy of the Vaccine in Syrian Hamsters" *Frontiers* 12: 720437.