International Journal for Quality Research 17(3) 707–728
ISSN 1800-6450

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Article info:
Received 21.06.2022.
Accepted 06.06.2023.

UDC – 005.6
DOI – 10.24874/IJQR17.03-06

REVIEW OF QUALITY CONTROL APPROACHES FOR BIOTECHNOLOGY-DERIVED VACCINES

Abstract: *This paper aimed to systematically review the quality control approaches for biotechnology-derived vaccines, including the covid vaccines. Google Scholar was used for selecting papers, which was limited to 28 to ensure that the review is not too long. From the 28 papers, 14 were reviews. There were only four research papers, of which, two were on covid vaccines. Thus, the diversity of the available quality control approaches was already limited. Many quality control tests are performed through the entire chain of sourcing to the end-user. Safety, purity, product integrity, efficacy, immunogenicity, and absence of side effects were the important quality control variables identified as critical for the effective use of vaccines, in most studies. This observation applies to covid vaccines also. As a self-check of the quality of the vaccine by the manufacturer may not be accepted by others, it is desirable to cross-check the reliability and validity of the factory quality test results through third-party testing. Often, despite all quality parameters being satisfactory, the vaccines fail in actual use. There could be a difference between the laboratory results and the real-world experiences of covid vaccines. The factors leading to this problem are not yet clear. International guidelines and standards help to ensure uniform quality of vaccines across the world facilitating the use of the same vaccines in different countries. This is evident from the covid vaccine exports from leading producer countries to other parts of the world. The essentiality of ensuring the proper quality of all vaccines, including covid vaccines, is clear from this review. The future is for the possibility of rapid quality tests facilitated by multiplex testing tools, non-animal testing, the use of plant-based vaccines aided by molecular farming, and larger-scale field evaluations of vaccines.*

Keywords: *Quality control approaches, Biotechnology-derived vaccines, Systematic review*

1. Introduction

Unlike chemical pharmaceuticals, biological products, including vaccines, are derived from living organisms with a molecular composition too complex to be defined by physical or chemical methods. Also, due to the inherent variability of living organisms, there is a high potential for their contamination with substances originating

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from starting materials or the environment. These factors necessitate special quality control and assurance mechanisms. The primary legal responsibility for the safety, quality, and efficacy of vaccines lies with the manufacturers, The national regulatory agencies have the responsibility of assuring the safety, quality, and efficacy of these vaccines, when released for use among populations.

In an informal consultation process at WHO (WHO, 2005), certain molecular methods of quality assurance were highlighted. In the quality control of live attenuated viral vaccines, genetic stability is of great concern. To address this problem, quantitative mutant analysis of viral quasi-species by polymerase chain reaction (PCR) and restriction enzyme cleavage' (MAPREC) were suggested. Other suggestions were the MAPREC test and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry MALDITOF mass spectrometry, a reverse genetics approach to decontaminate influenza A vaccines from wild-type viruses derived from non-validated systems, a three-step molecular process to test polio vaccines for quality, genome profiling for testing the authenticity of BCG vaccines, infectivity PCR to measure the potency of mumps, measles and rubella virus in trivalent measles, mumps, rubella (MMR) vaccines, a PCR-based reverse transcriptase (RTase) called PERT to detect adventitious retroviruses, PCR for testing the presence of extraneous agents in vaccines, tests for contamination of many vaccines with host DNA from cell substrates and residual DNA and molecular typing and algorithms.

The above-discussed WHO report shows the large range of biotechnological methods for quality control of vaccines. A slightly more focused topic for this review is ‘any’ quality control approach for ‘biotechnologically-derived vaccines.

1.1 What is a biotechnological vaccine?

Biotechnological vaccines are produced mainly using in three ways: separation of a pure antigen using a specific monoclonal antibody; synthesis of an antigen with the assistance of a cloned gene and synthesis of peptides to be used as vaccines (Chen, Cheng, Chen Yang, & Yeh, 2017). Meningococcus B (MenB) vaccine, hepatitis B (HB) vaccine, cholera vaccine, vaccines for diphtheria toxoid, and tetanus toxoid, Middle East respiratory syndrome (MERS) coronavirus, and the current Covid-19 vaccines are some examples produced using reverse vaccinology, recombinant subunit, recombinant protein, DNA and RNA biotechnologies. Having discussed some basics of vaccines above, this paper aims to review some more recent literature (2016-2022) on various quality control approaches for bio-technologically derived vaccines.

2. Methodology

Google Scholar was used for identifying the literature relevant to the review topic. The period was set as 2016-2022 to select more recent papers. This period was chosen arbitrarily. The papers were selected from the web pages based on whether they contain significant points about quality control approaches for biotechnological vaccines in general and covid vaccines in particular. This type of selection yielded 28 papers out of which 12 were general and the remaining 16 were about covid vaccines. It is recognised that there are many more papers on these topics. But the total number of papers was limited to 28 keeping in mind a reasonable length for the review.

Each paper is described below and then collated in the Discussion section to conclude in the next section. The sections on limitations of this review and scope for further research end this paper. A tabulated statement highlighting the main features of the selected papers is also provided in Table 1 (see Appendix).

3. Result

The protocols used for establishing and operating four independent biosafety level 2–3 units consisting of a specific pathogen-free breeding mouse colony, Hartley guinea pig colony, tissue culture, banking area, vaccine production, and vaccine quality control/quality assurance areas) used to produce vaccines against Argentinian haemorrhagic fever (AHF) caused by the Junín virus (JUNV), were described by Ambrosio, et al. (2018). Various quality control methods through the entire process, storage, and despatch have been described in the paper and a tabulated statement is also provided.

Frye, et al. (2016) pointed out that the regulatory agencies, instead of asking for assurance of clonality of the vaccine production cell lines, should ask for ensuring the quality of the vaccine administered to patients, and on ensuring process consistency, and implementing appropriate control strategies through the life cycle of the products.

The emergence of antimicrobial resistance (AMR) stimulated the research and development of alternatives to antibiotics. Bacteriophages have very desirable characteristics, such as their ability to propagate at the site of infection and low toxicity. But they have the drawbacks of limited host range and prevalence of phage-resistant bacterial mutants. Poor stability of phage cocktails has led to the large-scale failure of clinical trials in the past. Since phage propagation has to be done on bacteria, the challenge of their purification is also great. Regulations meant for strict quality control of viral vaccines apply to phage drugs also. The review by Mutti and Corsini (2019) addressed these issues and solutions offered by various researchers. Quality by Design (QbD) is the most effective concept to ensure the robustness of the process for the manufacture of consistently safe and effective drug products (DP). The QbD manufacturing starts with the identification of the Quality Target Product Profile (QTPP), which includes the intended clinical setting, administration route, dosage, container system, and storage of the DP. The QTPP delineates the biological, chemical, microbiological, and physical characteristics related to the Critical Quality Attributes (CQAs). For bacteriophage-based DP, the CQAs include identity, absence of contaminating phages, titres of each phage present in the cocktail, the maximum level of bacterial toxins and other contaminants, pH, sterility, and shelf life. Appropriate tests are available to ensure all these characteristics in the final phage drug. Total quality control and assurance system through the manufacture-to-end use stages is the final solution to the problems. Several organizations have succeeded in getting clinical trials approved by regulatory bodies with Good Manufacturing Practices (GMP) for phage cocktails. Cost reduction happens due to avoiding large-scale rejections of poor quality products, the cost of maintaining documents on deviations, registration costs for process changes, and the management of corrective and improvement actions (CAPA).

Some of the modern trends in the quality paradigm of biopharmaceutical products were discussed by Yu, Taraban, Wang, and Briggs (2017). Verification-based quality control using non-expert non-traditional evaluation in the clinical setting is fast emerging as a new method of ensuring the safety of biopharmaceutical products including vaccines. Non-destructive inspection methods like water-proton NMR (wNMR) are being used increasingly.

Agrobacterium-mediated gene transfer and transformation via genetically modified plant viruses are being used very commonly to produce effective vaccines. Some new approaches have been developed to increase the efficiency of former methods such as biolistic, electroporation, agroinfiltration,

sonication, and polyethylene glycol treatment. Plant-based vaccines have been produced for TB, avian influenza, Deng, Rabies, Hepatitis B, Foot, and Mouth disease (animals), diabetes, HIV, and Ebola viral diseases. Laere, et al. (2016) discussed some challenges and prospects in this respect.

Recently, there had been some accelerated regulatory approvals of Chimeric Antigen Receptor T-cell (CAR-T) therapies for refractory haematological malignancies. There is high potential for this novel technology platform to provide new therapeutic options in the areas of oncology, where the medical needs are largely unmet. These types of medicines are powerful 'living drugs.' Also, they are very different from the conventional small molecule and biologic therapies at several levels. The highly complex nature and varied composition of CAR-T-based products require a lot of research to develop the best approaches to ensure reproducible and cost-effective manufacture, clinical development, and application. The key issues related to manufacturing and quality control of these new therapeutic modalities were reviewed by Eyles, et al. (2019). Extensive in-process and quality control testing are involved during the manufacturing process of these products. Release tests need to confirm the identity, purity, safety, and potency of manufactured medicinal products. Manufacturers complain about the lack of standards, reference materials and performance controls to ensure reproducibility and interoperability of testing.

According to Kis, Shattock, Shah, and Kontoravdi (2019), the quality control in all the four promising vaccine manufacturing platforms consisting of yeast, ADDomer, Gamma, and RNA platforms, is done by structural characterisation of vaccine active ingredients like amino acid composition, partial amino acid sequencing, peptide mapping, lipid and carbohydrate structure, buoyant density, and epitope characterization. The methods used for these assessments are amino acid sequencing, Western blotting, gel electrophoresis, and HPLC. Routine checking of the antigenicity and sterility are also done before formulation. In the case of formulated vaccines, evaluations of protein and aluminium content, pyrogenicity, and in vivo potency (determined as ED50) are tested. For in-process quality control during manufacturing, temperature, pressure, pH, electric conductivity, the concentration of various components, homogeneity, and presence of chemical and biological contaminants are measured regularly and kept within their optimal ranges.

Observing that quality assurance of biopharmaceuticals requires higher levels of analytical effort compared to small molecules, Parr, Montacir, and Montacir (2016) provided an overview of the various analytical methods for characterization of protein biologicals. The reviewed analytical methods included classical methods like gel electrophoresis and liquid chromatography and modern mass spectrometric investigations. Full molecule investigations of native or denaturized proteins were also reviewed. Additionally, glycoprotein analysis using glycopeptide, released glycan, and monosaccharide analysis were reviewed.

Methods used for the detection (both initial detection and confirmation of contamination) and identification of the viral contaminant in cell culture operations, as tabulated by Barone, et al. (2020) included PCR, IVV, electron microscopy, viral genome sequencing, immunofluorescence, mass spectrometric protein sequencing, RNA fingerprinting, serology, and massively parallel sequencing. There were variations in the results showing contamination, some showing absence and others showing the presence of contamination for the same samples. These results imply that the safety of biological products should be ensured using more than one method including prevention, detection, and viral clearance throughout the manufacturing process.

The ICH quality guidelines were reviewed by Khagga, Kaitha, Dammu, and Mogili (2019) The items applicable for biotechnology products including vaccines, (even if vaccines are not specifically mentioned in some places) were Q5A (R1), Q5B to E, Q6 A, and B, Q7, Q9 to 11 and Q14. However, the years of ICH references listed at the end were not given.

In a detailed treatment related to advances made in the vaccine sector so far, Mao and Chao (2019) provided a diagrammatic presentation of certain important points. Those related to quality control are presented and discussed here.

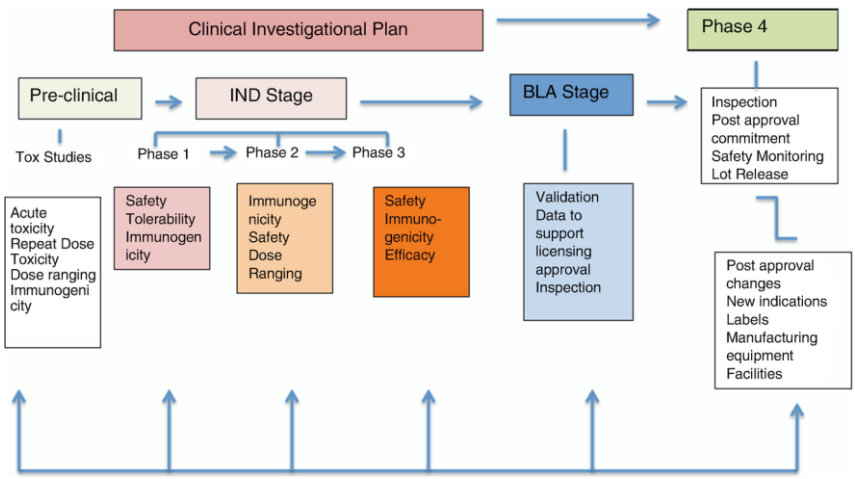

Figure 1. Stages of vaccine review and regulation (Mao & Chao, 2019)

Figure 1 describes the review and regulation processes including those related to quality control aspects mostly falling under the jurisdiction of the FDA Center for Biologics Evaluation and Research (CBER). The main technologies used for vaccine production, with examples, are Live attenuated bacteria and viruses (e.g., BCG, MMR, etc.), Inactivated bacteria and viruses (whole-cell pertussis, IPV, etc.), Proteins (e.g., diphtheria and tetanus toxoids), Polysaccharides (PneumoVax), Conjugated polysaccharides (meningococcal conjugate vaccine, PCV13), Virus-like particles (VLPs), Recombinant proteins, Application of mRNA and Adjuvant development and applications. Quality control steps are involved in the manufacturing process, end-product testing, and clinical trials on batches released for this purpose. During the manufacturing process, more than 50% of production time is usually dedicated to several hundred quality control tests as required before releasing a batch of vaccine products. These involve purification, detoxification, and QC testing of packed products. Demonstration of safety and effectiveness through clinical evaluation is important for getting the license for new vaccine manufacture. Phase 3 clinical trials should be conducted using clinical trial materials drawn from large-scale manufactured stocks to ensure the consistency of Phase 3 clinical materials with the commercial products. Clinical bridging studies also can be done for the same purpose. The quality control requirements for vaccine development and manufacture stages are different from those required for clinical stages.

Various aspects related to the prospects of mRNA vaccines were discussed by Jackson, Kester, Casimiro, Gurunathan, and DeRosa (2020). A greater understanding of quality attributes related to translation efficiency,

and comprehensive recognition of the importance of mRNA delivery influence a new era in vaccine development activities. Purification, sterility, identity, purity, and potency testing are parts of quality control in the case of RNA-based vaccines also. Some critical quality attributes of mRNA vaccines are given in Figure 2.

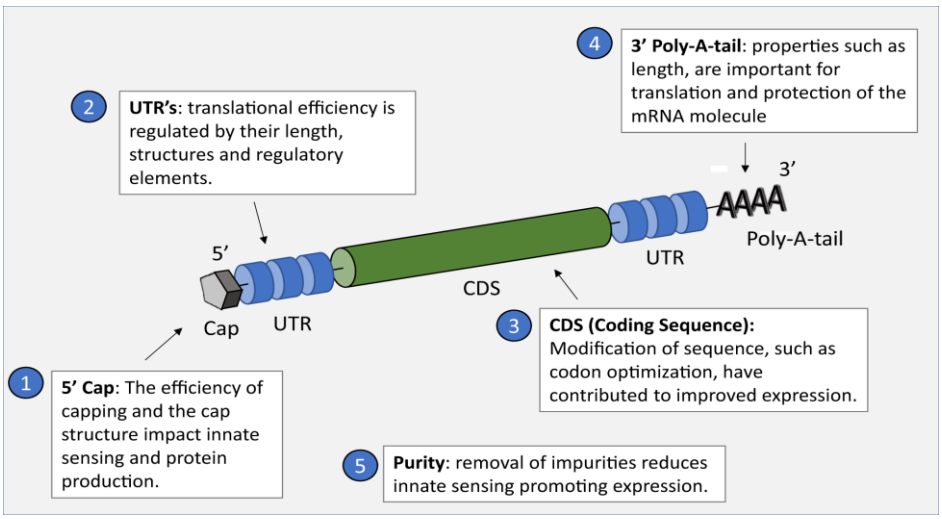

Figure 2. Critical quality attributes of mRNA vaccine performance (Jackson, Kester, Casimiro, Gurunathan, & DeRosa, 2020)

3.1 Quality control approaches for Covid-19 vaccines

Continuing with mRNA vaccines, Fang, et al. (2022) discussed the advances made in the development of mRNA vaccines against Covid-19. The key mechanism of the mRNA vaccine technology is based on a vehicle that enables the delivery of a nucleic acid molecule encoding the antigen of interest into the target cell in the human host. This enables the host cell to produce the target protein and express the antigen to elicit the immune response. Thus, upon invasion by a pathogen carrying the antigen, the immune system of the host can quickly trigger humoral and cellular immune responses to prevent the disease. The mRNA is a negatively charged and unstable molecule. Hence, it is usually encapsulated in a delivery vehicle to enter the target cell. The mRNA delivered by vaccine vehicles based on lipid nanoparticles (LNPs) enters cells exclusively by endocytosis, which forms an endosome without destroying the cell membrane. After entering the cytoplasm, the endosome is degraded at lysosomes. To ensure structural integrity and thus translation of injected mRNA, endosomal fusion with lysosomes and disruption need to be avoided. Different types of Covid-19 mRNA vaccines have been developed, as shown in Figure 3.

The mRNA vaccines can be classified into non-replicating mRNA, self-amplifying mRNA (saRNA), and circular RNA (circRNA) based on their genetic characteristics (Figure 3). Non-replicating mRNA vaccines deliver exclusively genetic information coding for the target antigen. The saRNA vaccines can deliver genetic information encoding the target antigen and other genes like viral RNA polymerase to enable self-replication of mRNA.

Recently, Covid-19 vaccines based on circRNA have been developed due to their

natural high stability. Most of the current Covid-19 vaccines are non-replicating mRNA vaccines. The circRNA vaccine seems to be efficient against the beta variant of coronavirus. Variations of circRNA configurations have been shown to protect against Omicron or Delta variant, but rarely both.

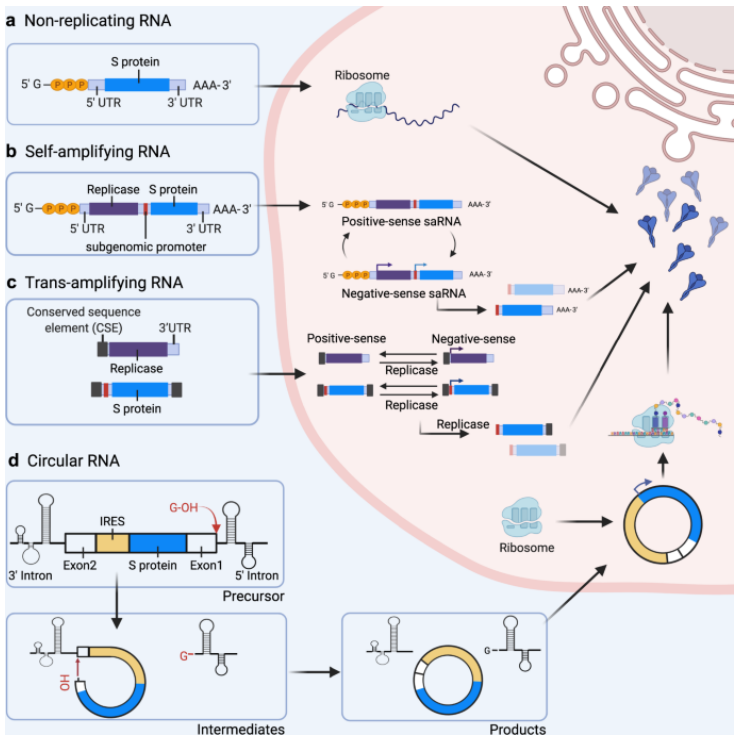

Figure 3. Different types of Covid-19 mRNA vaccines (Fang, et al., 2022)

Production of mRNA vaccines relies on in vitro synthesis technology instead of the conventional needs for culturing cells or viruses. This reduces the time to produce the vaccine to 10 days even on a large scale and reaches the market within another one month. Most manufacturing approaches are sophisticated. Hence, quality control of mRNA vaccine production is a challenge. Safety, efficacy, and quality control of vaccines are determined by measuring critical process parameters (CPPs) and intermediate critical quality attributes (IQAs). The management of LNP encapsulation is directly related to the quality of the final mRNA vaccine, particularly involving target gene sequence design, raw materials, mRNA purity and integrity, and mRNA/lipid ratio. Quality control of mRNA vaccines should adhere to criteria prescribed by laws and regulations of the producing countries. Quality control and quality management should be incorporated throughout the production process and life cycle of mRNA vaccines, thereby submitting the entire chain to stringent quality control monitoring. Quality control of COVID-19 mRNA vaccines focuses on raw materials like plasmids, biobanks, lipids, nucleotides, and enzymes used in the production process, semi-finished, and final product. Low-temperature storage is essential to maintain the quality for a long time.

The need for assessing the safety profile of covid vaccines through clinical trials spreading over four phases first was

highlighted by Calina, et al. (2020). The difference between the development of normal and covid vaccines and their testing requirements in each phase are presented in Figure 4.

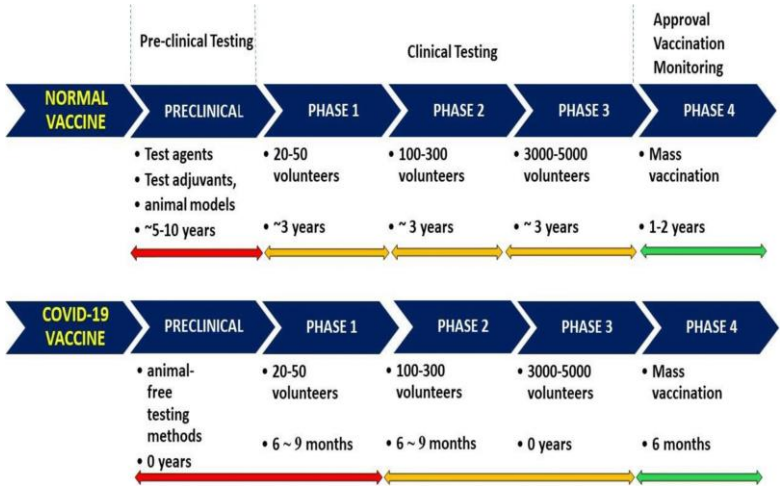

Figure 4. Comparison of normal and covid vaccine development phases and their quality testing requirements (Calina, et al., 2020)

Figure 4 reveals a considerable shortening of the duration of testing at each phase of the vaccine development. Against the normal period of about 20 years required, covid vaccines are being developed and become ready for mass vaccination within two years.

In a review, Calina, et al. (2020) showed that, even with the reduction in duration of trial phases and the testing requirements, efficacy, duration of protection and effectiveness were important quality parameters to approve a covid vaccine for common use.

A detailed review of the Chinese attempts to develop, manufacture, quality control, and globally distribute covid vaccines was done by Huang, Fu, and Wang (2022). For quality control, China relied on national vaccine quality control laboratories. Technical guidelines were prepared for various aspects related to the covid vaccine. The quality control laboratories undertook inspections. Scientific research institutions studied and developed relevant animal models, quality control methods, reference materials, and quality specifications for innovative vaccine R&D for COVID-19 soon after the outbreak. Through laboratory work, such as virus seed verification, cell bank verification, product verification, and clinical serum testing, safety and effectiveness were ensured. For evaluation of vaccine efficacy as part of quality control, the NIFDC established a SARS-CoV-2 neutralization assay based on a pseudo-typed SARS-CoV-2 virus at the beginning of the outbreak and a transgenic mouse model. These evaluation tools were used in preclinical and clinical evaluations of the vaccine candidates. Because of its flexibility and availability, the covid pseudo-virus was employed widely in the investigation of infectivity and antigenicity of covid variants, to facilitate the assessment of the current vaccine efficacy against the circulating variants and to design future broad-spectrum vaccines for the continuing pandemic. To ensure the emergency use of covid vaccines, 13 provincial drug quality control agencies were authorized to undertake the lot release tasks and quality

assurance for vaccine inoculation in China.

In another review, Kim, Marks, and Clemens (2021) pointed out that vaccine quality is often taken for granted. However, even minor lapses in quality can affect the safety and efficacy of the vaccines. Apart from country-specific regulatory requirements of quality, there are international guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), EU, and OECD for ensuring quality in clinical research. ICH Q series provides guidelines for ensuring that vaccine quality meets global standards for its chemistry, manufacturing, and control. Failure to meet the quality standard can attract legal, ethical, scientific, and regulatory consequences. Yet, some scientific questions like optimum dose, schedule, efficacy, effectiveness, herd immunity, and boosting safety remain. Surveillance of new strains and their impacts is also a major issue.

The need to evaluate different covid-19 vaccines against multiple endpoints and variants in a range of subgroups in effectiveness studies was stressed by Hungerford and Cunliffe (2021). If done properly, it will provide ample workload for public health and academics shortly. It is possible to use test negative case-control designs with common protocols of routine, quality controlled, health and surveillance data systems with harmonisation to reduce costs. As new infections are reduced, case-control studies can be replaced with cohort studies for better precision. Such studies offer opportunities to explore indirect effects of vaccination, including herd protection, and the effects of covid vaccines on non-specific outcomes, such as absenteeism from work or school, and symptoms such as gastrointestinal illness despite certain methodological limitations. Studies on the efficacy of covid vaccines across age groups backed by their health status data are required for precise evaluation of various parameters related to vaccine efficacy.

Each platform of vaccine development and production needs to be regarded as a separate product and process with specific quality considerations. The review by Verdecia, et al. (2021) discussed the relevant platforms for developing covid vaccines and the advantages and disadvantages of each. The most important quality aspect is that the 12- to an 18-month timeline of corona vaccines suffers from deficient safety and effectiveness studies in every demographic category, whatever may be the age, race, ethnicity, or gender.

Dror, et al. (2020) noted that suspicions about the quality, efficiency, and safety of covid vaccines have led to the hesitancy among certain people to receive covid vaccines. Survey studies showed that parents, nurses, and medical workers not caring for the covid-positive patients had high levels of vaccine hesitancy. These results emphasize the need for educating even medical professionals to vaccinate against infectious diseases.

Contrary to the survey results of Dorr et al. (2020) showing large-scale vaccine hesitancy among the Israeli population, the results of the survey by Wang, et al. (2020) showed that over 90% of the Chinese population preferred covid vaccination, of whom, about 50% wanted the vaccine safety to be confirmed before vaccination. An immunization schedule was preferred over emergency vaccination. Being male, being married, high-risk perception, previous influenza vaccination, belief in vaccine efficacy, or accepting of doctor's recommendations increased the probability of accepting covid vaccination as soon as possible. Confirmed or suspected cases in local areas, vaccination convenience, or vaccine price were the negative factors against acceptance of immediate vaccination.

The main quality variables for which the appropriate tests are required were discussed by Haque and Pant (2020). First, the validity of a candidate vaccine needs to be assessed by an evaluation of humoral, cellular, and

functional immune responses appropriate for each of the included COVID-19 antigens. Measurement of cellular responses should be done using CD8+ and CD4+ T cell responses. The functional activity of immune responses needs to be tested in vitro neutralization assays using wild-type virus or pseudo-virus. True efficacy should be assessed by challenging infections, but in the absence of a cure, ethical questions of this remain. After this, the clinical signs need to be monitored for protection or manifestation of unintended toxic effects. The likelihood of the vaccine inducing some respiratory pathology in humans should be assessed by post-vaccination animal challenge studies. The type of nonclinical and clinical immune responses induced by the vaccine candidate need to be determined. A vaccine, whether fully or partially protective, should lower the "R" value (viral reproduction number), for effective control of the disease spread.

Busquet, Hartung, Pallocca, Rovida, and Leist (2020) stressed the importance of using animal-free testing methods to assess the safety, efficacy, and quality of covid vaccines for rapid release of vaccines to control the pandemic as early as possible.

As a part of quality control, the real-world effectiveness of covid vaccines is important. The methodological approaches for this were reviewed by Teerawattananon, et al. (2022) to select the most appropriate approaches for implementation in low- and middle-income countries (LMICs). Most studies (97.5%) were conducted in high-income countries and the majority of them assessed mRNA vaccines (78% mRNA only, 17% mRNA and viral vector, 2.5% viral vector, 2.5% inactivated vaccine). A majority of the studies (83%) used a cohort study design. The major limitations of these studies were the short follow-up time, limited assessment, and mitigation of potential confounders, including previous infection and healthcare-seeking behaviour.

The quality control variables of immunogenicity, efficacy, safety, tolerability and the long-term efficacy covid vaccines are critical, according to Kudlay and Svistunov (2022) based on a review. Solutions for the potential methodologic challenges of using the commonly applied test-negative case-control design for evaluating COVID-19 vaccines were suggested by Patel, Jackson, and Ferdinands (2020). Some unknown effects of the vaccines requiring specific quality control tests are the magnitude of protection across demographic subgroups of the population, underlying health conditions, the duration of protection, comparative evaluations of vaccine types, assessments of 1 vs 2 doses of vaccination, effectiveness against genetic variants and mutants of the coronavirus and a more comprehensive understanding of safety and rare complications.

Baldwin, et al. (2021) reviewed the challenges of developing vaccine analytical tools rapidly during the current covid pandemic, the need to address the possible redundancy and unreliability of the current analytical methods due to progressive virus mutation and adaptation, and the potential of computer-modeling techniques to model and analyse key viral proteins and their attributes to assist vaccine production and assay design. The current range of analytical tools, vitro assays for immunogen characterization to assays to measure vaccine responses in vivo, available for covid vaccine application is also reviewed. The future perspectives of covid vaccine analytical tools over the next 5–10 years have also been predicted. The analytical tool development process of the ongoing covid pandemic has been presented in Figure 5.

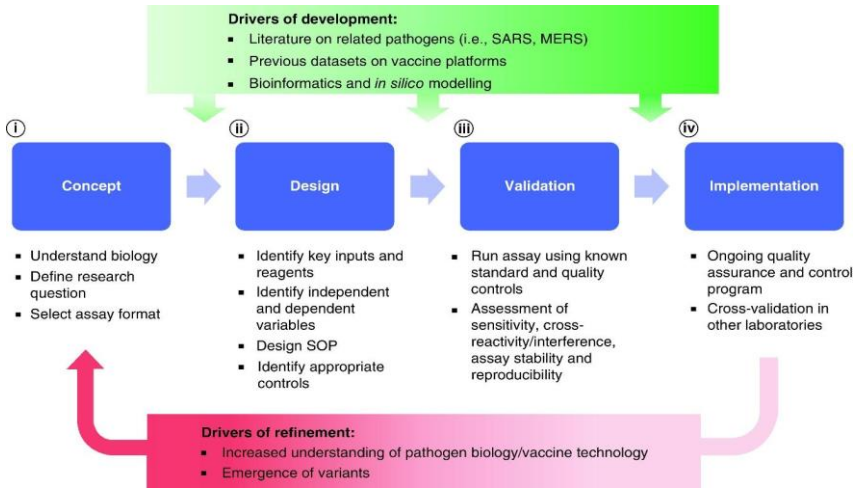

Figure 5. The process of analytical tool development for quality control during the covid pandemic (Baldwin, et al., 2021)

The analytical tools covered in this review are the methods of vaccine characterisation, purity (contamination) determinations, safety, specific tools for the viral characterisation of mRNA and other vaccines, different types of immunogenicity, and animal models for efficacy evaluations and virus quantification in various tissues. Multiplex analytical formats have been predicted for the future.

The variables related to the post-regulatory approval testing by independent laboratories for the additional assurance of the safety and quality of a product, especially in the UK, usually include an evaluation of potency, purity, product identity, and RNA integrity. No animal-based tests are required. In the parallel testing by the manufacturers and the UK government laboratories, the completion of the latter earlier than the former provides the opportunity for the manufacturer to review production and quality control assessment methods. The independent testing of covid vaccines before their market availability is a critical and impartial quality and safety assurance step (Rose, Stickings, Schepelmann, Bailey, & Burns, 2021).

4. Discussion

Out of the total 28 papers, 18 were reviews, five were discussion papers including one of the explanations using diagrams, one was an editorial and four were research papers. Of the four research papers, two were related to covid vaccines. There were 14 country-specific papers, dominated by China, the USA, and the UK. Others were general or dealt with more than one country.

The papers generally discussed quality control as a part of the manufacturing process aimed at regulatory approvals. Both in-process and final product quality tests were done routinely. The tests consisted of physical, chemical, biochemical, and other methods. The most-reported quality control variables were purity, safety, efficacy, product integrity, immunogenicity, absence or minimum side effects, long-term effectiveness, and tolerance.

Some specific quality control points were biological, chemical, microbiological, and physical characteristics related to the Critical Quality Attributes (CQAs), absence of toxins, shelf-life and storage temperature, third-party quality testing, proper standards, guidelines, reference materials and

performance controls, computer-based modelling applications for product design, multiple tests for contamination detection, duration of protection and effectiveness, herd immunity, mutants and variants of coronavirus, factors related to the hesitancy for covid vaccination, immune responses and real-world effectiveness.

These findings prove that undoubtedly, quality control issues are more complex than it seems on the surface.

5. Conclusion

The essentiality of ensuring the proper quality of all vaccines, including covid vaccines, is clear from this review. Many quality control tests are performed through the entire chain of sourcing to the end-user. Safety, purity, product integrity, efficacy, immunogenicity, and absence of side effects are important for the effective use of vaccines, especially those related to covid. It is desirable to cross-check the reliability and validity of factory quality test results through third-party testing. Often, despite all quality parameters being satisfactory, the vaccines fail in actual use. There is a difference between the laboratory results and the real-world experiences of covid vaccines. The factors leading to this problem are not yet clear. International guidelines and standards help to ensure uniform quality of vaccines across the world facilitating the use of the same vaccines in different countries. This is evident from the covid vaccine exports from leading producer countries to other parts of the world. The future is for the possibility of rapid quality tests facilitated by multiplex testing tools, non-animal testing, the use of plant-based vaccines aided by molecular farming, and larger-scale field evaluations of vaccines.

5.1 Scope for future research

Most of the research on quality control approaches for covid vaccines was done in developed countries. There should be more research in developing countries on this aspect. The reasons for the quality-compliant vaccines failing in-field use need to be explored through systematic research. The development of rapid quality analytical tools should continue to take it forward. More research on multiplex testing tools to facilitate rapid quality testing needs to be done. Vigorous research is required on plant-based vaccine manufacture backed by molecular farming. Separate research on molecular farming is also needed.

5.2 Limitations of this review

For this review, only one search engine, Google Scholar, was used. If databases were used, more useful papers may have been possible. The number of papers to be selected was pre-decided based on the desired length of this paper. If no such restrictions were placed, many more papers would have been reviewed. Papers dealing directly with quality control approaches were very rare. In most papers, the topic was a part of the development and manufacturing processes. Most papers were reviews and discussion papers. There were only four research papers, of which, two were on a covid vaccine. More research papers could not be included due to this problem.

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Appendix

Table 1. Papers includes in the review

No.	Reference & country	Aim	Method	Findings	Remarks
1	Ambrosio, A. M., Mariani, M. A., Maiza, A. S., Gamboa, G. S., Fossa, S. E., & Bottale, A. J. (2018). Protocol for the production of a vaccine against argentinian hemorrhagic fever. In *Hemorrhagic Fever Viruses* (pp. 305-329). Humana Press, New York, NY. DOI: 10.1007/978-1-4939-6981-4_24. ARGENTINA	Describe the full manufacture and quality control processes for the entire range of Argentinian haemorrhagic fever vaccine production to sales.	Description with diagrams, photos and tables.	The quality controls used in processes adequately described	The descriptions are more on in-process quality control, which is essential for quality assurance.
2	Frye, C., Deshpande, R., Estes, S., Francissen, K., Joly, J., Lubiniecki, A., ... & Anderson, K. (2016). Industry view on the relative importance of "clonality" of biopharmaceutical-producing cell lines. *Biologicals*, *44*(2), 117-122. DOI: 10.1016/j.biologicals.2016.01.001 . USA	To present the industry view on the importance of clonality in vaccine production and quality control.	Review paper	The regulatory agencies, instead of asking for assurance of clonality of the vaccine production cell lines, should ask for ensuring quality of the vaccine actually administered to patients, and on ensuring process consistency and implementing appropriate control strategies through the life cycle of the products.	This is a one-sided view.
3	Mutti, M., & Corsini, L. (2019). Robust approaches for the production of active ingredient and drug product for human phage therapy. *Frontiers in Microbiology*, 2289. DOI: 10.3389/fmicb.2019.02289. AUSTRIA.	Robust approaches for manufacture and quality control of human phage therapy products.	Review paper	Using the concepts of Quality by Design (QbD) and GMP for phage products largely lead to phage products eligible for clinical trials.	QbD is an attractive concept for vaccine production and quality control also.
4	Yu, Y. B., Taraban, M. B., Wang, W., & Briggs, K. T. (2017). Improving biopharmaceutical safety through verification-based quality control. *Trends in biotechnology*, *35*(12), 1140-1155. DOI: 10.1016/j.tibtech.2017.08.010. USA.	Review of non-traditional and non-clinical methods of verification-based quality control.	Review paper	The 21st Century Cures Act encourages more data collection by nonexperts in non-traditional clinical trial settings (Real-World Data). Non-destructive inspection technologies, like wNMR, are in the development stage. .	The discussed trends are interesting.
5	Laere, E., Ling, A. P. K., Wong, Y. P., Koh, R. Y., Mohd Lila, M. A., & Hussein, S. (2016). Plant-based vaccines: production and challenges. Journal of Botany, 4928637. DOI: 10.1155/2016/4928637. MALAYSIA	Review of challenges and problems in manufacture and quality control of plant-based vaccines.	Review paper	New approaches that enhance the efficiencies of vaccines produced using Agrobacterium-mediated gene transfer and challenges and problems are discussed.	Emerging trends in this field are interesting.

6	Eyles, J. E., Vessillier, S., Jones, A., Stacey, G., Schneider, C. K., & Price, J. (2019). Cell therapy products: focus on issues with manufacturing and quality control of chimeric antigen receptor T-cell therapies. *Journal of Chemical Technology & Biotechnology*, *94*(4), 1008-1016. DOI: 10.1002/jctb.5829. UK.	Review of manufacture and quality control of cell therapy products involving T-cell antigens.	Review paper	Extensive in-process and quality control testing are involved during the manufacturing process of these products. Release tests need to confirm the identity, purity, safety and potency of manufactured medicinal products. Manufacturers complain on the lack standards, reference materials and performance controls to ensure reproducibility and interoperability of testing.	T-cells are important in immune-oncology.
7	Kis, Z., Shattock, R., Shah, N., & Kontoravdi, C. (2019). Emerging technologies for low-cost, rapid vaccine manufacture. *Biotechnology journal*, *14*(1), 1800376. DOI: 10.1002/biot.201800376. UK	To assess the merits and quality control methods involved in four vaccine manufacturing platforms.	Research paper	Six parameters were used to evaluate the platforms of yeast, ADDomer, Gamma and RNA for vaccine production. Methods used for various in-plant quality control and final product quality assessments were described.	Some emerging technologies are interesting.
8	Parr, M. K., Montacir, O., & Montacir, H. (2016). Physicochemical characterization of biopharmaceuticals. *Journal of pharmaceutical and biomedical analysis*, *130*, 366-389. DOI: 10.1016/j.jpba.2016.05.028. GERMANY	To provide an overview on analytical methods for characterization of protein biologicals.	Review paper	The reviewed analytical methods included classical methods like gel electrophoresis and liquid chromatography and modern mass spectrometric investigations. Full molecule investigations of native or denaturized proteins were also reviewed. Additionally, glycoprotein analysis using glycopeptide, released glycan and monosaccharide analysis were reviewed.	Only a very limited number of methods were reviewed.
9	Barone, P. W., Wiebe, M. E., Leung, J. C., Hussein, I., Keumurian, F. J., Bouressa, J., ... & Springs, S. L. (2020). Viral contamination in biologic manufacture and implications for emerging therapies. *Nature biotechnology*, *38*(5), 563-572. DOI: 10.1038/s41587-020-0507-2. MULTICOUNTRY	To collect data on these events. This study provides key industry insights into the commonly viral contaminants, along with their sources, the cell lines affected, corrective actions, as well as the impact that such events can have.	Research paper	Methods used for the detection (both initial detection and confirmation of a contamination) and identification of the viral contaminant of a virus contamination in cell culture operations, as tabulated by (Barone, et al., 2020) included PCR, IVV, electron microscopy, viral genome sequencing, immunofluorescence, mass spectrometric protein sequencing, RNA fingerprinting, serology and massive parallel sequencing. There were variations in the results showing contamination, some showing negative while others showing positive for the same samples. These results imply that the safety of biologic products should be ensured using more than one method including prevention, detection and viral clearance throughout the manufacturing process.	

10	Khagga, B., Kaitha, M. V., Dammu, R., & Mogili, S. (2019). ICH guidelines–"Q" series (quality guidelines)-A review. *GSC Biological and Pharmaceutical Sciences*, *6*(3), 089-106. DOI: 10.30574/gscbps.2019.6.3.0034. INDIA.	To review the ICH guidelines.	Review paper	There were 12 ICH guidelines related to quality control in biotechnological products including vaccines.	The years of publication of ICH guidelines listed at the end were not given.
11	Mao, H. H., & Chao, S. (2019). Advances in vaccines. *Current Applications of Pharmaceutical Biotechnology*, 155-188. DOI: 10.1007/10_2019_107. GENERAL	To review the developments in manufacture and quality control of vaccines over the years.	Review paper	Vaccine review and regulation takes place over several stages including quality control tests. Over the course of the manufacturing process, over 50% of production time is usually dedicated to several hundred quality control tests prior to releasing a batch of vaccine products. These involve purification, detoxification and QC testing of packed products. Demonstration of safety and effectiveness through clinical evaluation is important for getting license for new vaccine manufacture. Phase 3 clinical trials should be conducted using clinical trial materials drawn from large-scale manufactured stocks to ensure the consistency of Phase 3 clinical materials with the commercial products. Clinical bridging studies also can be done for the same purpose. The quality control requirements for vaccine development and manufacture stages are different from those required for clinical stages.	There are some interesting diagrams.
12	Jackson, N. A., Kester, K. E., Casimiro, D., Gurunathan, S., & DeRosa, F. (2020). The promise of mRNA vaccines: a biotech and industrial perspective. *npj Vaccines*, *5*(1), 1-6. DOI: 10.1038/s41541-020-0159-8. GENERAL	To discuss the promise of mRNA vaccines and its manufacturing and quality control issues.	Discussion paper	A greater understanding of quality attributes related to translation efficiency, and a comprehensive recognition of the importance of mRNA delivery influence a new era in vaccine development activities. Purification, sterility, identity, purity, and potency testing are parts of quality control in the case of RNA-based vaccines also. There are some critical quality requirements mRNA vaccines.	The discussion on mRNA leads to the quality control issues of Covid-19 vaccines.
13	Fang, E., Liu, X., Li, M., Zhang, Z., Song, L., Zhu, B., ... & Li, Y. (2022). Advances in COVID-19 mRNA vaccine development. *Signal Transduction and Targeted Therapy*, *7*(1), 1-31. DOI: 10.1038/s41392-022-00950-y. CHINA	To review and discuss the development, manufacture and quality control aspects of Covid-19 mRNA vaccines.	Discussion paper	Various aspects related to mRNA technology, its application to Covid-19 vaccine production and quality control have been discussed in detail with diagrams where required.	A good paper on Covid-19 vaccine and latest developments of the disease and control.

14	Calina, D., Sarkar, C., Arsene, A. L., Salehi, B., Docea, A. O., Mondal, M., ... & Sharifi-Rad, J. (2020). Recent advances, approaches and challenges in targeting pathways for potential COVID-19 vaccines development. *Immunologic research*, *68*(6), 315-324. DOI: 10.1007/s12026-020-09154-4. MULTICOUNTRY.	To review the recent advances in the development and quality controls of covid vaccines.	Review paper	The need for assessing the safety profile of covid vaccines through clinical trials spreading over four phases first was highlighted. Considerable shortening of the durations of testing at each phase of the vaccine development.	The basics have been explained well.
15	Calina, D., Docea, A. O., Petrakis, D., Egorov, A. M., Ishmukhametov, A. A., Gabibov, A. G., ... & Tsatsakis, A. (2020). Towards effective COVID-19 vaccines: Updates, perspectives and challenges. *International journal of molecular medicine*, *46*(1), 3-16. MULTICOUNTRY.	To review the perspectives and challenges in covid vaccine development and quality control.	Review paper	Apart from the reduction in durations of trial phases and the testing requirements, efficacy, duration of protection and effectiveness were important quality parameters to approve a covid vaccine for common use.	
16	Huang, Z., Fu, Z., & Wang, J. (2022). Review on drug regulatory science promoting COVID-19 vaccine development in China. *Engineering*, 10(March), 127-132. DOI: 10.1016/j.eng.2022.01.001. CHINA.	To review of the Chinese attempts to develop, manufacture, quality control and globally distribute covid vaccines.	Review paper	For quality control, China relied on national vaccine quality control laboratories. Technical guidelines were prepared for various aspects related to covid vaccine. The quality control laboratories undertook inspections. Scientific research institutions studied and developed relevant animal models, quality control methods, reference materials, and quality specifications for innovative vaccine R&D for COVID-19 soon after the outbreak. Through laboratory work, such as virus seed verification, cell bank verification, product verification, and clinical serum testing, the safety and effectiveness were ensured. For evaluation of vaccine efficacy as part of quality control, the NIFDC established a SARS-CoV-2 neutralization assay based on a pseudo-typed SARS-CoV-2 virus at the start of the outbreak and a transgenic mouse model. These evaluation tools were used in preclinical and clinical evaluations of the vaccine candidates. Because of its flexibility and availability, the covid pseudo-virus was employed widely in the investigation of infectivity and antigenicity of covid variants , to facilitate assessment of the current vaccine efficacy against the circulating variants and to design future broad-spectrum vaccines for the continuing pandemic. To ensure the emergency use of covid vaccines, 13 provincial drug quality control agencies were authorized to undertake the lot release tasks and quality assurance for vaccine inoculation in China.	One of the few papers in which quality control has been given a separate section, albeit being brief.

17	Kim, J. H., Marks, F., & Clemens, J. D. (2021). Looking beyond COVID-19 vaccine phase 3 trials. *Nature medicine*, *27*(2), 205-211. DOI: 10.1038/s41591-021-01230-y. GENERAL.	To review quality issues beyond phase 3 clinical trials.	Review paper	Vaccine quality is often taken for granted. However, even minor lapses in quality can affect safety and efficacy of the vaccines. Apart from country-specific regulatory requirements of quality, there are international guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), EU and OECD for ensuring quality in clinical research. ICH Q series provides guidelines for ensuring that vaccine quality meets global standards for its chemistry, manufacturing and control. The inability to meet the quality standard can attract legal, ethical, scientific and regulatory consequences. Yet, some scientific questions like optimum dose, schedule, efficacy, effectiveness, herd immunity and boosting safety remain. Surveillance of new strains and their impacts is also a major requirement.	Good discussion on international efforts.
18	Hungerford, D., & Cunliffe, N. A. (2021). Real world effectiveness of covid-19 vaccines. *bmj*, *374*. DOI: 10.1136/bmj.n2034. GENERAL	The real situation of covid vaccines, quality control and vaccination in the world.	Editorial	There is need to evaluate different covid-19 vaccines against multiple endpoints and variants in a range of subgroups means that effectiveness studies. . If done properly, it will provide ample workload for public health and academic for the foreseeable future. It is possible to use test negative case-control designs with common protocols of routine, quality controlled, health and surveillance data systems with harmonisation to reduce costs. As new infections are reduced, case control studies can be replaced with cohort studies for better precision. Such studies offer opportunities to explore indirect effects of vaccination, including herd protection, and the effects of covid-19 vaccines on non-specific outcomes, such as absenteeism from work or school and symptoms such as gastrointestinal illness despite certain methodological limitations. Studies on efficacy of covid vaccines across age groups backed by their health status data are required for precise evaluation of various parameters related to vaccine efficacy.	A good paper dealing with quality well.
19	Verdecia, M., Kokai-Kun, J. F., Kibbey, M., Acharya, S., Venema, J., & Atouf, F. (2021). COVID-19 vaccine platforms: Delivering on a promise?. *Human Vaccines & Immunotherapeutics*, *17*(9), 2873-2893. DOI: 10.1080/21645515.2021.1911204. GENERAL.	Discussions about the uniqueness of covid vaccine platforms and the associated quality requirements to vaccinate majority of the global population.	Review paper	Each platform of vaccine development and production needs to be regarded as a separate product and process with specific quality considerations. The most important quality aspect is that the 12- to 18-month timeline of corona vaccines suffers from deficient safety and effectiveness studies in every demographic category, whatever may be the age, race, ethnicity, or gender.	Stress on the demographic aspects along with quality.

20	Dror, A. A., Eisenbach, N., Taiber, S., Morozov, N. G., Mizrachi, M., Zigron, A., ... & Sela, E. (2020). Vaccine hesitancy: the next challenge in the fight against COVID-19. *European journal of epidemiology*, *35*(8), 775-779. DOI: 10.1007/s10654-020-00671-y. ISRAEL.	To evaluate vaccine hesitancy among different demographic categories of Israeli population.	Research paper	Suspicions about the quality, efficiency and safety of covid vaccines has led to the hesitancy among certain people to receive covid vaccines. Survey studies showed that parents, nurses, and medical workers not caring for the covid-positive patients had high levels of vaccine hesitancy. These results emphasize the need for educating even medical professionals to vaccinate against infectious diseases.	First research paper.
21	Haque, A., & Pant, A. B. (2020). Efforts at COVID-19 vaccine development: challenges and successes. *Vaccines*, *8*(4), 739. DOI: 10.3390/vaccines8040739. USA.	To discuss the challenges of covid vaccine development and how quality control challenges can be addressed.	Discussion paper	Methods of evaluating the validity, efficacy functional activity, clinical signs, safety and immune responses were discussed.	Good discussion about quality aspects. No quantitative data.
22	Wang, J., Jing, R., Lai, X., Zhang, H., Lyu, Y., Knoll, M. D., & Fang, H. (2020). Acceptance of COVID-19 Vaccination during the COVID-19 Pandemic in China. *Vaccines*, *8*(3), 482. DOI: 10.3390/vaccines8030482. CHINA.	To evaluate the acceptance of covid vaccination in China and give suggestions for vaccination strategies and immunization programs	Research paper	Over 90% of the Chinese population preferred covid vaccination, of whom, about 50% wanted the vaccine safety to be confirmed before vaccination. An immunization schedule was preferred over emergency vaccination. Being male, being married, high risk perception, previous influenza vaccination, belief in vaccine efficacy or acceptance of doctor's recommendations increased the probability of accepting covid vaccination at the earliest. Confirmed or suspected cases in local areas, vaccination convenience or vaccine price were the negative factors against acceptance of immediate vaccination.	Second research paper
23	Busquet, F., Hartung, T., Pallocca, G., Rovida, C., & Leist, M. (2020). Harnessing the power of novel animal-free test methods for the development of COVID-19 drugs and vaccines. *Archives of toxicology*, *94*(6), 2263-2272. DOI: 10.1007/s00204-020-02787-2. GENERAL.	To discuss about the importance of using animal free testing methods for quality control of covid vaccines.	Discussion paper	The paper stressed on the importance of using animal free testing methods to assess the safety, efficacy and quality of covid vaccines for rapid release of vaccines to control the pandemic as early as possible.	Some novel thoughts
24	Teerawattananon, Y., Anothaisintawee, T., Pheerapanyawaranun, C., Botwright, S., Akksilp, K., Sirichumroonwit, N., ... & Isaranuwatchai, W. (2022). A systematic review of methodological approaches for evaluating real-world effectiveness of COVID-19 vaccines: Advising resource-constrained settings. *PloS one*, *17*(1), e0261930. DOI: 10.1371/journal.pone.0261930GENERAL	To review the methodological approaches for evaluating real world effectiveness of covid vaccines.	Review paper	The majority of the studies (97.5%) were conducted in high-income countries and the most of them assessed mRNA vaccines (78% mRNA only, 17% mRNA and viral vector, 2.5% viral vector, 2.5% inactivated vaccine). A majority of the studies (83%) used a cohort study design. The major limitations of these studies were the short follow-up time, limited assessment and mitigation of potential confounders, including previous infection and healthcare seeking behaviour.	Useful information
25	Kudlay, D., & Svistunov, A. (2022). COVID-19 Vaccines: An Overview of Different Platforms. *Bioengineering*, *9*(2), 72. DOI:10.3390/bioengineering9020072. GENERAL.	To review different platforms of covid vaccine production and its quality control aspects.	Review paper	The quality control variables immunogenicity, efficacy, safety, tolerability and the long term efficacy covid vaccines are critical.	Average quality paper.

26	Patel, M. M., Jackson, M. L., & Ferdinands, J. (2020). Postlicensure evaluation of COVID-19 vaccines. *JAMA*, *324*(19), 1939-1940. DOI: 10.1001/jama.2020.19328. GENERAL.	To review the quality control variables to be evaluated after the vaccine has been put to use among the population.	Review paper	Some unknown effects of the vaccines requiring specific quality control tests are the magnitude of protection across demographic subgroups of population, underlying health conditions, the duration of protection, comparative evaluations of vaccine types, assessments of 1 vs 2 doses of vaccination, effectiveness against genetic variants and mutants of the coronavirus and a more comprehensive understanding of safety and rare complications.	Average quality paper
27	Baldwin, J., Piplani, S., Sakala, I. G., Honda-Okubo, Y., Li, L., & Petrovsky, N. (2021). Rapid development of analytical methods for evaluating pandemic vaccines: a COVID-19 perspective. *Bioanalysis*, *13*(24), 1805-1826. DOI: 10.4155/bio-2021-0096. GENERAL.	To review the analytical tools used for evaluating covid vaccines.	Review paper	The common analytical tools used for various determinations and a few specific analytical tools for covid vaccine have been discussed. The future is for multiplex analytical formats.	A paper exclusively dealing with quality control analytics.
28	Rose, N. J., Stickings, P., Schepelmann, S., Bailey, M. J., & Burns, C. (2021). National control laboratory independent lot testing of COVID-19 vaccines: the UK experience. *npj Vaccines*, *6*(1), 1-4. DOI: 10.1038/s41541-021-00368-7. UK.	The importance of independent testing of covid vaccines is discussed.	Discussion paper	The variables related to the post regulatory approval testing by independent laboratories for the additional assurance of the safety and quality of a product, especially in UK, usually includes an evaluation of potency, purity, product identity, and RNA integrity. No animal-based tests are required. In the parallel testing by the manufacturers and the UK government laboratories, the completion of the latter earlier than the former provides opportunity for the manufacturer to review production and quality control assessment methods. The independent testing of covid vaccines before their market availability is a critical and impartial quality and safety assurance step	Another paper exclusively discussing quality control analytics.