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REVIEW ARTICLE

Navigating the Transition: A Scoping Review of System-Level Factors in Biosimilar Integration for Immune-Mediated Inflammatory Diseases

Shania Kumar[1] · **Nicola Dalbeth**[1,2] · **Chiara Gasteiger**[1,3]

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Abstract

Background Patients with immune-mediated inflammatory diseases are routinely transitioned from originator biologics to biosimilars to reduce healthcare costs. While barriers related to patient and practitioner beliefs and knowledge are well-documented, less focus has been placed on system-level factors that may hinder biosimilar uptake.

Aims This review aims to identify system-level factors that impact biosimilar brand transitions for treatment of immune-mediated inflammatory diseases, as reported by key stakeholders involved in real-world brand changes.

Methods A scoping review was conducted following the Arksey and O'Malley framework and was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for scoping reviews (PRISMA-ScR). A comprehensive search was performed in APA PsycInfo, Embase, PubMed, Scopus, and Web of Science, and databases for major conferences in rheumatology, dermatology, and gastroenterology. Data from relevant studies were extracted and summarized onto a structured coding sheet before being synthesized.

Results Of 2301 articles screened, 47 journal articles and five conference abstracts were included. Most studies were conducted in the United States and focused primarily on rheumatology. Barriers and facilitators were organized into four overarching themes. These were regulatory and approval processes (e.g., tendering practices, interchangeability policies, prescriber guidelines), healthcare system policies and incentives (including quotas, insurance coverage, reimbursement mechanisms, and rebates), infrastructure and logistics (such as supply chain considerations and storage requirements), and communication and education (including media and expert influence and the involvement of patient organizations).

Conclusions Multiple components of the healthcare system play a role in successful biosimilar transitions. Leveraging regulations, policies, infrastructure, and communication before, during, and after transition offers a practical blueprint for managing brand changes across health systems and therapies.

1 Introduction

Immune-mediated inflammatory diseases, such as inflammatory arthritis, are chronic, debilitating conditions that lead to numerous adverse outcomes, including depression and reductions in quality of life [1]. Biopharmaceuticals (biologics) have greatly improved

Key Points

Stakeholders' knowledge and perceptions can hinder the uptake of biosimilars.

System-level factors may also impact biosimilar use in immune-mediated diseases.

Barriers include delayed tenders, administrative burdens, and storage logistics.

Facilitators include gainsharing, clear guidance, and market share targets.

✉ Chiara Gasteiger
chiara.g@auckland.ac.nz

[1] Department of Medicine, University of Auckland, Auckland, New Zealand

[2] Department of Rheumatology, Health New Zealand, Auckland, New Zealand

[3] School of Community and Public Health, AUT University, Auckland, New Zealand

the management of immune-mediated inflammatory diseases, but their high costs present a major barrier to patient access globally. Biosimilars are biological products that closely resemble an original biologic drug and are manufactured after its patent expires, offering a cost-effective alternative without compromising safety or efficacy. These therapies promote brand-to-brand competition, helping to lower costs and enhance patient access to essential treatments. For instance, in the United States (US), biosimilars have led to cost reductions of 20–30% [2]. Biosimilars differ from small-molecule generics in both development and production costs. Development takes 7–8 years and requires analytical, preclinical, and clinical studies to demonstrate biosimilarity, resulting in costs of 100–250 million US dollars (USD) [3, 4]. These high fixed costs, along with marginal costs (e.g., distribution and manufacturing costs) constrain price competition and slow market penetration [5], leading to smaller discounts than generics.

Between 2006 and 2022, the European Medicines Agency (EMA) approved 86 biosimilars [6], and by 2025, the Food and Drug Administration (FDA) had approved 70 [7], with other regulatory bodies also following suit. With many more biologics approaching the end of their patent, biosimilars are set to continue playing a growing role in the treatment of various immune-mediated inflammatory diseases. Globally, healthcare providers are prescribing biosimilars to biologic-naïve patients, while patients already using original biologics are being transitioned to biosimilars in an effort to reduce healthcare expenditure.

Regulatory agencies like the FDA, EMA, Therapeutic Goods Administration, and Medicines and Healthcare Products Regulatory Agency have developed specialized pathways to facilitate the approval and market entry of biosimilars. For example, in the US, the FDA serves as the central regulatory authority for biosimilars through its Center for Drug Evaluation and Research. The FDA evaluates analytical, preclinical, and clinical evidence to determine biosimilarity and interchangeability, issues guidance documents to clarify evidentiary standards, and grants licensure under the Biologics Price Competition and Innovation Act (BPCIA) [8]. It also oversees post-marketing surveillance and pharmacovigilance to ensure long-term safety and efficacy [9].

While substantial research has confirmed biosimilar safety and efficacy and explored stakeholders' perceptions of biosimilars [10–13], less is known about how to effectively integrate these treatments into healthcare systems without disrupting care. A recent study in New Zealand found that rheumatology patients transitioning to the adalimumab biosimilar reported low satisfaction, citing issues such as a lack of patient care supplies (e.g., alcohol wipes), the loss of patient support programs, and inadequate training on the new auto-injector device [14]. Healthcare providers also encountered challenges, particularly with the initial authorization process and inadequate communication from health agencies [15]. Such experiences mirror dissatisfaction from other biosimilar brand transitions globally (e.g., [16]), underscoring the importance of carefully managing these transitions to foster trust and support the sustained uptake of biosimilars.

Moreover, regulatory and policy challenges can affect the integration and use of biosimilars. Although medicine regulators generally follow similar approaches to approving biosimilars, variations in policies (particularly regarding substitution, testing, and indication extrapolation) can delay or impede access to these cost-effective therapies [17]. For example, regions with policies that support product-specific guidance, indication extrapolation, shorter exclusivity periods, and substitution have seen higher rates of biosimilar approval and uptake [17].

It is crucial to understand the barriers and facilitators influencing the successful integration of biosimilars into healthcare systems. International comparisons may provide valuable insights into the integration of biosimilars into diverse healthcare systems. For instance, Europe has a long-standing history with biosimilars, beginning with the approval of Omnitrope (somatropin) in 2006, and so has already generated some evidence on effective policies and implementation strategies [18]. Similarly, a regulatory pathway for biosimilars was created in 2010 in the US, with the US BPCIA being signed into law as part of the Affordable Care Act in 2010. As such, there has been some recent focus on overcoming challenges related to low switching in the US [19]. Lessons from countries with different healthcare models, such as single-payer systems versus private insurance systems, could also help inform strategies for integrating biosimilars globally. This scoping review identifies and summarizes key literature on the process of transitioning to biosimilars for treatment of immune-mediated inflammatory diseases, focusing on the system-level factors in real-world brand changes. While the specific functions and policies of regulatory agencies (e.g., FDA and EMA) differ, the current review focuses on identifying how stakeholders have perceived and engaged with system-level factors rather than analyzing the regulatory systems themselves. System-level factors are defined as characteristics in the broader economic and political context of healthcare systems and organizations, including policies, regulations, payer structures, and institutional practices that shape biosimilar uptake, beyond influences at the individual patient or clinician level [20].

2 Methods

A systematic scoping review was conducted to examine the breadth and nature of existing literature in this area, as no comprehensive synthesis across global healthcare systems has previously been undertaken. The review follows Arksey and O'Malley's [21] five-step process for scoping reviews. The steps are (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting the data, and (5) collating, summarizing, and reporting results. The review is reported in line with the extended Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for scoping reviews (PRISMA-ScR) [22] and was pre-registered in Open Science Framework (OSF) [23].

2.1 Identifying the Research Question

An initial search of the literature revealed a substantial number of studies addressing patients' and providers' perceptions of biosimilars, as well as real-world transitions that underscore their safety and efficacy. However, there has been no comprehensive scholarly review exploring the systemic factors related to these brand transitions, particularly regarding the logistical aspects of such changes. To address this gap, we applied the Exploration, Preparation, Implementation, Sustainment (EPIS) framework [24] to guide our scoping review and organize the evidence across the full transition process. Our focus is specifically on outer context factors such as health system policies, service environments, and institutional infrastructure that influence biosimilar brand changes before, during, and after implementation. This framework provides a structured lens to assess how broader system-level influences interact with the practical realities of biosimilar adoption. As such, the research question was as follows: what are key system-level factors that impact biosimilar brand transitions for treatment of immune-mediated inflammatory diseases, as reported by key stakeholders involved in real-world brand changes?

2.2 Identifying Relevant Studies

The following databases were systematically searched to identify relevant articles: APA PsycInfo, Embase, PubMed, Scopus, and Web of Science. The most recent conferences held in 2023 and 2024 were also searched to identify recent studies that have not been published (e.g., United European Gastroenterology Week, European Crohn's and Colitis Organisation, European League Against Rheumatism, Digestive Diseases Week, American College of Rheumatology Annual Meeting, World Congress of Dermatology, and World Congress in Ophthalmology). Search terms were collaboratively developed with input from all authors and a subject librarian. Free-text and index terms were used, including "biosimilar pharmaceuticals," "follow on biologics," "drug substitution," "switch," "organization and administration," and "health care delivery." The search strategy was adapted for databases as necessary (see the Supplementary Tables 1–7, for the final search strategies).

2.3 Selecting Studies

Search results were initially exported into RefWorks, and duplicates were removed before being exported to Rayyan, where further duplicates were identified and removed [25]. One author (SK) made the initial selections on Rayyan based on screening study titles and abstracts. Further selections were made by reviewing the entire article. A second author (CG) also independently reviewed 25% of the abstracts/titles and 28% of the full-text articles, and inter-rater agreement was calculated. Conference abstracts underwent a similar screening process, with one author (SK) conducting the initial review and a second author (CG) independently assessing approximately 50 abstracts. Additionally, reference lists from the final selection of articles were examined to identify potentially relevant studies that may have been missed or incorrectly indexed in the databases. Any disagreements were resolved through discussion until full consensus was obtained.

To be eligible for inclusion, studies had to explore outcomes related to the process of changing from a bio-originator to a biosimilar, such as satisfaction with the authorization process. Patients were receiving biologics in the specialist fields of rheumatology, dermatology, gastroenterology, or ophthalmology. There were no restrictions on age, as both children and adults may be transitioned to biosimilars. Studies were published from 2006 onwards (as this is when the first biosimilar was approved by the EMA) in English and could employ any research design (e.g., experimental, observational, or qualitative research). Any studies that did not meet these criteria were excluded. See Supplementary Table 8 for the full inclusion and exclusion criteria.

2.4 Charting the Data

Key information pertaining to the study's characteristics (publication year, design, methods, and country reviewed) was extracted into a structured Excel sheet. Details about the population (e.g., population type [e.g., patient, policy maker, multistakeholder], sample size, clinical specialization) and the biological treatments involved were also extracted. Facilitators and barriers to biosimilar uptake were extracted as outcomes, including regulatory and approval processes, healthcare system policies and incentives, infrastructure,

logistics, and education. No formal quality assessment was undertaken as this was not the focus of the review.

2.5 Collating, Summarizing, and Reporting Results

A synthesis was undertaken to identify and analyze the key barriers and facilitators influencing the adoption of biosimilars for immune-mediated inflammatory diseases. This analysis included an exploration of factors such as regulatory policies, healthcare system infrastructure, physician and patient education, and economic incentives.

2.6 Compliance with Ethics Guidelines

This review utilized data from previously conducted studies without patient-level data; thus, institutional review board approval was not required. Three studies included in the review were conducted by ND and CG; however, they did not participate in the data extraction process for these studies.

3 Results

3.1 Study Selection

The systematic search process identified 2301 records from databases (Fig. 1). From these, 749 were removed due to being duplicates. During the screening of the title and abstract, an additional 1461 articles were removed, with a 93% (360/388) agreement rate between the raters. A further 47 articles were removed during full-text screening (88% agreement rate [23/26] between raters). In addition, 116 abstracts were screened from seven major conferences held in 2023 and 2024, with a 94% (51/54) agreement rate between raters. The reference lists of the included abstracts were also reviewed for additional relevant papers, yielding an additional three articles. A total of 47 journal articles and five conference abstracts were included in the review (see the Spplementary Material for the full list).

Studies were published between 2014 and 2024 (Supplementary Table 9). Most studies focused on the US (n = 15). Eight studies examined multiple countries, while seven did not specify a country. Three studies examined each of Belgium, France, the United Kingdom (UK), Canada, and New Zealand, and two examined Spain. Additionally, single studies explored Lebanon, Hungary, Mexico, Sweden, and Brazil. Most studies (n = 15) focused exclusively on rheumatology, with only one study dedicated to gastroenterology. Twenty-one studies did not report a specialization, while 15 studies examined biosimilar use in multiple specializations (e.g., gastroenterology, rheumatology, and dermatology). Studies primarily involved multi-stakeholder groups (n = 20), patients (n = 15), physicians (n = 7), pharmacists (n = 5), or policy experts (n = 2). Three studies utilized data from sales, pharmacy claims, or community pharmacies.

Most studies were quantitative (n = 36), followed by qualitative (n = 10), with six studies employing a mixed methods design. Among the quantitative studies, the majority were cross-sectional (n = 25), including one that incorporated a discrete choice experiment. Seven studies used a retrospective observational or cohort design, three used prospective cohort or longitudinal designs, and one adopted a quasi-experimental approach. The mixed methods studies commonly combined surveys with qualitative interviews or other open-ended components. As most studies were descriptive (primarily cross-sectional surveys and qualitative investigations), these focused on stakeholder attitudes and perceived barriers rather than analyses designed to estimate effect sizes or causal impacts. A smaller subset used more rigorous observational methods, including cohort studies. Only one study employed a quasi-experimental interrupted time series design capable of supporting a causal inference.

3.2 Themes

Four overarching themes were identified relating to system-level factors that impact the transition from innovator biologics to biosimilars for treatment of immune-mediated inflammatory diseases. These were (1) regulatory and approval processes, (2) healthcare system policies and incentives, (3) infrastructure and logistics, and (4) communication and education campaigns. Figure 2 illustrates the facilitators and barriers that should be considered before, during, and after the transition to a biosimilar to support and improve the overall process.

3.2.1 Theme 1: Regulatory and Approval Processes

This theme explores the influence of regulatory agencies, such as the EMA and the FDA, on the adoption of biosimilars. It also examines how factors like tendering practices, interchangeability policies, and prescriber guidelines shape the uptake and utilization of biosimilars.

3.2.1.1 Regulatory Agencies Various stakeholders (physicians, hospital pharmacists, nurses, patient representatives, and regulators) across Europe emphasized the importance of unbiased information about biosimilars from independent bodies, such as the EMA and national competent authorities [26]. For example, EMA and European Commission biosimilar guidance documents were recognized as important, impartial resources of information. In another study, regulators across Europe emphasized the need for closer collaboration between the European Union and national regulatory

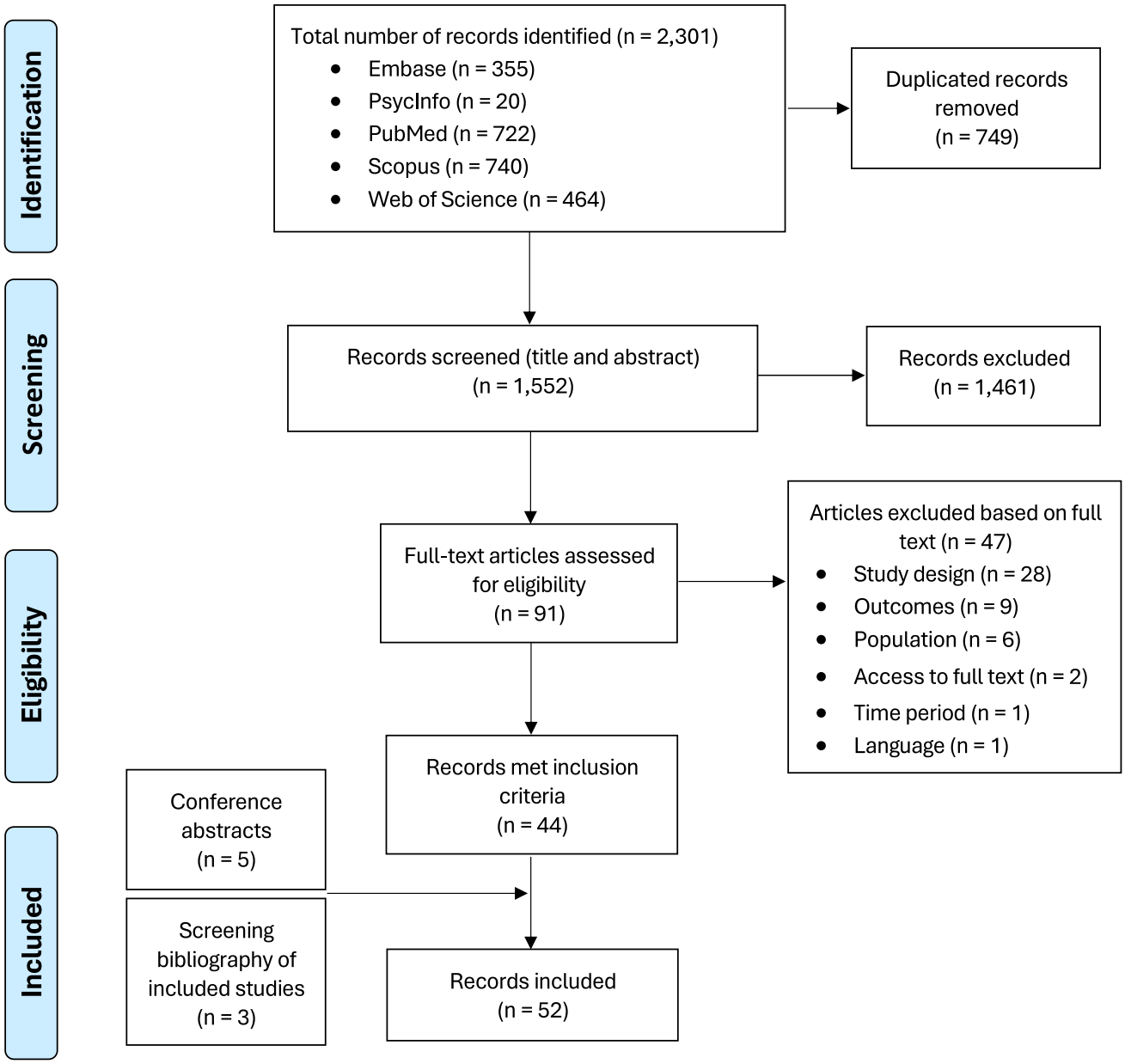

Fig. 1 PRISMA-ScR flowchart showing the study identification and screening process.

authorities to ensure homogenous information on biosimilars [27].

While authorities, physicians, pharmacists, and industry experts in Belgium expressed trust in the EMA's registration procedures, some physicians were skeptical about the agency's regulatory decisions [28]. Experts across Europe also identified a key barrier to biosimilar uptake: while the EMA possesses all the data for biologics, it does not make decisions regarding biosimilar substitution as this responsibility lies with individual member states [29]. In another study, an academic suggested the responsibility of interchangeability and biosimilar substitution should be transferred from national authorities in Europe to the EMA, given that the agency is responsible for possessing and evaluating all the data [28]. Meanwhile, in the US, 26% of 300 pharmacy professionals believed the FDA should continue to eliminate barriers to reduce the time between biosimilar approval and market availability [30].

3.2.1.2 Tendering Italian, Portuguese, and Spanish experts expressed concerns that the current tendering process, focused mainly on price and often allowing only a single

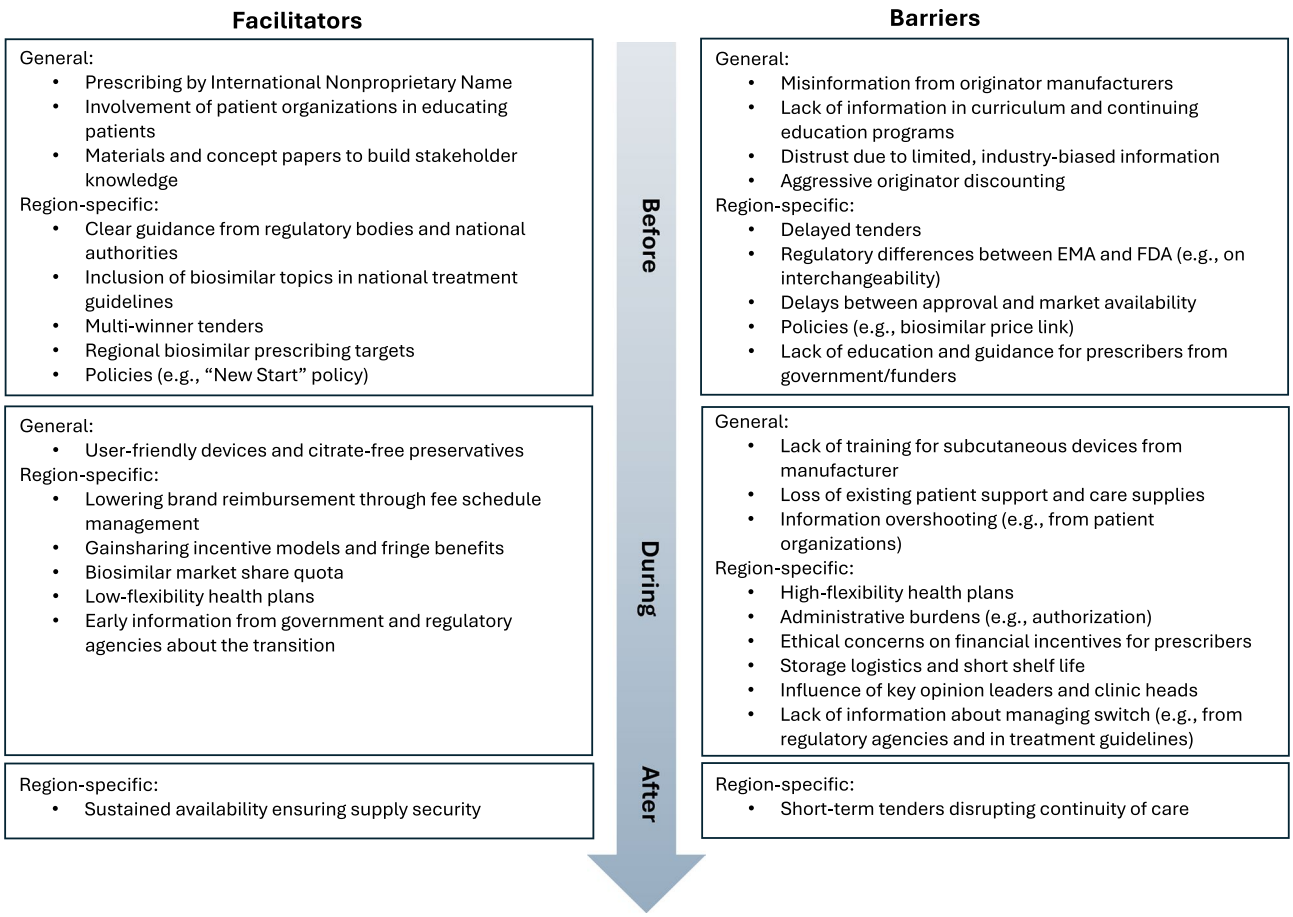

Fig. 2 General and region-specific system-level barriers and facilitators influencing the transition from a reference biologic to a biosimilar, as identified in this review, organized by the stage of implementation (before, during, and after the change). *EMA* European Medicines Agency, *FDA* Food and Drug Administration

supplier, may threaten long-term sustainability by creating supply instability, excessive price pressure, and reduced cost savings [31]. In addition, as tenders are awarded to a single winner, allowing biosimilars to compete in the same lot as bio-originators can affect therapeutic continuity for patients being treated with an originator [31]. Experts in these countries also reported that short-term hospital tenders (less than 1 year) have led to the need for parallel purchasing procedures to meet demand, ultimately driving up costs and limiting the ability of biosimilars to generate cost savings.

In Europe, hospital pharmacists, purchasers, and suppliers called for clearer guidelines on whether tenders should be reopened each time a new biosimilar enters the market [32]. Opening tenders when the first biosimilar is launched could potentially limit market opportunities for future entrants of the same product. Multi-stakeholders in this study recommended dividing the market between multiple suppliers, providing a commercial opportunity for multiple suppliers, and promoting plurality in the market to generate more sustainable tender practices. However, for this approach to be effective, healthcare systems and purchasing authorities would need the necessary tools to support a multi-winner tender structure [32]. Tenders were also reported to occasionally be delayed unnecessarily, possibly due to ongoing contracts with originator suppliers that are still valid at the time of biosimilar market entry [32].

3.2.1.3 Interchangeability In one US study involving 500 patients with rheumatoid arthritis, psoriasis, psoriatic arthritis, or inflammatory bowel disease, the majority were open to pharmacist-led substitution of a biosimilar for its reference biologic [33]. However, participants wanted this substitution to be communicated to themselves and their doctor (51%), or just themselves (19%), or their doctor (19%). Legally, only four US states prohibit pharmacists from substituting an interchangeable biologic without prior approval from the prescriber [33].

Physicians, hospital pharmacists, nurses, patient representatives, and regulators across Europe reported that the differing approaches of the EMA and FDA regarding

interchangeability have generated distrust among stakeholders [26]. For example, the FDA framework implied that some biosimilars are more similar to the reference drug than others. Multiple physicians and pharmacists also wanted the EMA to address interchangeability by issuing a clear position or requesting switch studies like the FDA's approach [26]. However, views on interchangeability studies were mixed. While some regulators and pharmacists considered such studies unnecessary and a misuse of resources, others supported them for providing additional data on sequential switching. In the US, physicians were particularly unified in their opposition to pharmacist substitution of interchangeable biologics without prior prescriber approval [34].

3.2.1.4 Prescriber Guidelines In the US, most states require that prescribers be notified when a biosimilar is substituted for its reference biologic [33]. Regulators and hospital pharmacists in Italy, Portugal, and Spain supported the use of regional biosimilar prescribing targets for biologic-experienced patients as a means to promote cost rationalization within hospitals [31]. Vogler and Schneider [35] noted that prescribing by International Nonproprietary Name (INN) facilitates biosimilar uptake and is implemented in 35 European countries, as well as in Canada and South Africa, with other countries also mandating its use. However, INN prescribing is not permitted in Austria, Denmark, Serbia, or Sweden.

3.2.2 Theme 2: Healthcare System Policies and Incentives

This theme explores how healthcare system policies, such as insurance coverage, reimbursement, and payer authorization, influence the uptake of biosimilars among different healthcare systems and countries. It also considers the economic incentives for healthcare providers, including price reductions and rebates, and examines how national economic and social contexts affect biosimilar use, particularly across different healthcare systems.

3.2.2.1 Healthcare System Policies McClean et al. [36] reported that the "New Start" policy in Canada led to a gradual increase in the proportion of biosimilar etanercept prescriptions of 0.65% per month (95% confidence interval [CI] 0.44–0.85). In comparison, after the mandatory switching policy, there was a sustained increase in the proportion of dispensed biosimilar etanercept and infliximab prescriptions of 76.98% (95% CI 75.56–78.41) and 58.43% (95% CI 52.11–64.75), respectively. In Europe, 15 of 42 countries apply a pricing strategy known as a "biosimilar price link," which ties the price of biosimilars to that of the originator biologic [35]. In most of these countries, the price gap between biosimilars and originator biologics is smaller than the gap typically seen between generics and their reference drugs, suggesting that biosimilars tend to have relatively higher prices. Additionally, regulators and hospital pharmacists in Italy, Portugal, and Spain reported that national biosimilar policies have successfully supported biosimilar uptake in acute care settings and helped overcome initial resistance to switching [31].

3.2.2.2 Incentives Physician specialists and hospital pharmacists in Belgium reported a lack of incentives from the perspective of physicians to prescribe biosimilars [37]. Of note, physician specialists and hospital pharmacists in Belgium challenged the idea of direct financial incentives to physicians who prescribed biosimilars. This was perceived as questionable from an ethical perspective, compensation was considered insufficient for the time spent with the patient, and the additional administrative burden was not outweighed by the financial compensation [37]. Similarly, Barbier et al. [27] found physicians, hospital pharmacists, nurses, patients, and regulators across Europe considered direct financial incentives on an individual level to be inappropriate. Instead, Barbier et al. [32] and Edgar et al. [38] both reported that gainsharing (allocating part of the savings to improve patient care and hiring pharmacy, nursing, or social worker staff) was seen as acceptable. Physicians, nurses, and some regulators across Europe reported that a tangible incentive to compensate stakeholders for biosimilar use would be appropriate due to the significant planning and time associated with switching [27]. Pharmacy professionals in the US recommended increasing reimbursement and lowering brand reimbursement through fee schedule management to overcome barriers to biosimilar adoption [30].

Physician specialists and hospital pharmacists in Belgium reported that pharmaceutical companies may offer direct informal incentives to physicians, which may affect physician decision-making [37]. Authorities, physicians, pharmacists, patients, academics, and industry experts in Belgium reported that in addition to discounts, manufacturers of biologics offer additional benefits to hospitals called fringe benefits. Benefits such as job promotions, sponsoring, and additional services for physicians and patients may increase physician loyalty and impact prescribing behavior [28].

3.2.2.3 Quotas In Italy, Spain, and Portugal, National Health Service (NHS) hospitals that attain 20% uptake of new biosimilar entrants within a year can reinvest 15–25% of the generated savings. However, failure to reach this quota can result in penalties [31]. Moorkens et al. [29] reported that Germany and Belgium utilize quotas to facilitate biosimilar uptake. In Belgium, where prescribing quotas were utilized, there was a smaller reduction in expenditure compared to France, which did not use quotas for infliximab biosimilars [39]. Barbier et al. [37] reported biosimilar market share quota was recommended by physician specialists and hospital pharmacists in Belgium to promote biosimilar uptake.

3.2.2.4 Economic and Social Context Baji et al. [40] reported that 92% of 51 gastroenterologists in Hungary were willing to consider biosimilars if specific benefits related to reimbursement were provided. If patients benefit from the cost savings produced by biosimilars (e.g., savings ensure continuous medicine supply or enable treatment of more patients), gastroenterologists are more likely to prescribe biosimilars [40]. In Belgian hospitals, lowering of biologic reimbursement for which a biosimilar is available has been reported by hospital pharmacists, purchasers, and suppliers [27]. In Belgium, manufacturers of originator biopharmaceuticals typically offer discounts that surpass the price difference of biosimilars. In contrast, biosimilar manufacturers generally do not provide discounts [28]. Pharmacy professionals in the US reported that biosimilar manufacturers need to negotiate contracts that counteract the significant rebates current biologics offer. For example, biosimilar manufacturers should enter the market with more competitive discounts off the average wholesale price [30]. Hospital pharmacists, purchasers, and suppliers in Europe reported that originator manufacturers often significantly reduced prices to maintain market share. Although these reductions reflect the intended competitive effect, the authors noted that they can both limit biosimilar uptake and drive other suppliers out of the market, especially when originators continue to be preferentially selected in tendering processes [32].

In the US, setting of care and insurance plans also influence biosimilar use. In one study, patients treated in an office setting were significantly less likely to switch to infliximab biosimilar compared to those treated in an outpatient hospital setting (odds ratio [OR] 0.178; $p < 0.01$; CI 0.151–0.209) [41]. In addition, enrollment in a low-flexibility health plan was associated with a higher likelihood of switching to a biosimilar (1% higher, $p < 0.01$) or initiating (2% higher, $p < 0.01$) biosimilar treatment compared to high-deductible plans [42]. The authors argue that although the effect size may appear small, when switchers make up only 3% of the population, this effect corresponds to a 33% increase in the likelihood of switching to a biosimilar. In contrast, high-flexibility plans were associated with a lower likelihood of switching (0.9% lower, $p < 0.01$) or initiating biosimilar treatment (1% lower, $p < 0.01$) when compared with high-deductible plans [42]. In addition, Roberts et al. [43] and Roberts et al. [44] found that the switching rate to biosimilar infliximab and adalimumab was higher in US patients with Medicaid or private insurance in comparison to US patients with Medicare. Specifically for infliximab, the rate of switching was significantly higher for patients with Medicaid (incident rate ratio [IRR] = 1.96, 95% CI 1.38–2.77) or private insurance (IRR = 1.95, 95% CI 1.51–2.54) compared to Medicare [43].

3.2.3 Theme 3: Infrastructure and Logistics

This theme focuses on the practical aspects of the transition from bio-originators to biosimilars. Subthemes include the administrative burden, medical device aspects such as the usability of injection devices (e.g., autoinjectors), supply chain logistics, and storage requirements.

3.2.3.1 Administrative Burden Both Gasteiger et al. [15] and Moorkens et al. [45] highlighted the increased physician workload due to the transition. Gasteiger et al. [15] specifically reported that the initial authorization process significantly contributed to this burden. Pharmacists frequently encountered dispensing errors due to incorrect linkage of authority numbers to the appropriate biosimilar brand, necessitating additional verification and, in some cases, direct contact with prescribers. In addition, the authors demonstrate that higher satisfaction with administrative workload ($p < 0.001$) (along with training for the biosimilar device [$p = 0.020$]) predicted satisfaction following the adalimumab biosimilar transition ($F = 12.68$, $R^2 = 0.51$, $p < 0.001$). Similarly, Edgar et al. [38] noted that simplifying prior authorization procedures was considered essential by experts to facilitate broader biosimilar uptake.

3.2.3.2 Device for Subcutaneous Biosimilars Three studies reported that inadequate training for biosimilar devices posed a barrier across multiple stakeholder groups, including rheumatologists, rheumatology nurses, and pharmacists [14–16]. In a large patient survey, 21% of 899 individuals with immune-mediated inflammatory diseases indicated they had not received sufficient training on the new adalimumab biosimilar device [16]. Concerns regarding the switching process were also common among hospital pharmacists in Italy, Portugal, and Spain, particularly for patients self-administering subcutaneous biologics [31].

Findings regarding injection pain associated with subcutaneous biosimilar devices were mixed. In some cases, the biosimilar device was perceived as an improvement over the originator. Rheumatologists and nurses reported that the citrate-free formulation of the adalimumab biosimilar reduced injection-site pain and improved ease of use, thereby supporting patient acceptance [15]. Similarly, in a study of 120 patients with rheumatoid arthritis or Crohn's disease, 82% preferred the biosimilar device over the originator, citing reduced pain or a lack of burning sensation as key reasons [46]. Conversely, concerns about pain and uncertainty around device composition were also evident. Renton et al. [47] reported that patients with juvenile idiopathic arthritis expressed anxiety about the potential reintroduction of citrate in biosimilar formulations. In contrast to positive

reports, Kaneko et al. [16] found that increased injection pain was the most commonly reported problem following the switch from originator to biosimilar among patients with various immune-mediated inflammatory diseases. Notably, patients who reported receiving adequate training on the new device were less likely to experience pain on administering the biosimilar (OR 0.20, 95% CI 0.07–0.55), reported fewer side effects (OR 0.17, 95% CI 0.06–0.47), and had less difficulty in using the new device (OR 0.25, 95% CI 0.15–0.41) [16].

Several features of subcutaneous biosimilar devices were identified as facilitators of successful transitions. Patients reported a preference for the biosimilar's user-friendly administration, ease of learning, and pen design [46]. Specific attributes such as the color indicator, viewing window size, and buttonless activation were particularly well-received. In a US-based survey, Giavatto et al. [48] found that pharmacists working in rheumatology, dermatology, and gastroenterology considered device-related factors important when selecting a biosimilar for substitution, including injection device design (42%), availability of a citrate-free formulation (37%), latex-free components (19%), needle size (9%), and high-dose concentration (9%). Complementing these findings, Barbier et al. [27] reported that physicians and regulators across Europe believed biosimilars have the potential to enhance care delivery through improvements in administration devices and the development of novel administration routes.

3.2.3.3 Storage Requirements Physicians in the US managing intravenous infusions for rheumatology, dermatology, and gastroenterology noted that non-medical switching could pose logistical challenges, as multiple medications would need to be maintained on site [49]. Given the relatively short shelf life of biopharmaceuticals and the necessity for stringent distribution and storage conditions, hospitals may incur additional financial burdens when required to stock both bio-originators and biosimilars concurrently [28]. Supporting this, 21% of pharmacists practicing in these specialties in the US reported that product storage considerations influenced their choice of biosimilar for substitution [48]. Furthermore, patients with juvenile idiopathic arthritis expressed concerns about potential disruptions to home delivery processes, particularly due to the requirement that biosimilars be refrigerated [47].

3.2.3.4 Funding for Patient Support Infrastructure In two studies, rheumatology patients, rheumatologists, rheumatology nurses, and pharmacists in New Zealand reported the need for a comparable patient support program to that provided by bio-originator manufacturers [14, 15]. In a separate study, pharmacists also indicated they would like to refer patients to patient support groups organized by the manufacturer [50].

3.2.3.5 Supply Chain Logistics In New Zealand, rheumatology patients, rheumatologists, nurses, and pharmacists expressed satisfaction with the continued availability of biosimilars following the switch to an adalimumab biosimilar [14, 15]. However, satisfaction was markedly lower regarding the availability of ancillary supplies, such as alcohol wipes and sharps bins, after the brand transition. In Europe, pharmacists perceived that the introduction of biosimilars was an opportunity to enhance supply security amid concerns about potential shortages [27]. Correspondingly, in the US, 40% of pharmacists in rheumatology, dermatology, and gastroenterology reported that supply chain factors influenced their selection of biosimilars for substitution [48].

3.2.4 Theme 4: Communication and Education Campaigns

This theme highlighted the role of education in promoting biosimilar adoption. Specifically, it examined the level of stakeholder knowledge about biosimilars and their uptake in different healthcare systems. It also identified the need for educational programs and campaigns for providers, as well as the provision of patient support programs.

3.2.4.1 Media and Expert Influence Moorkens et al. [45] found that, in Sweden, the attitudes of key opinion leaders and clinic heads could either support or hinder biosimilar adoption. Adoption was encouraged when they trusted the efficacy and cost-effectiveness of biosimilars and adhered to local guidelines. Conversely, uptake was hindered when they prioritized treatment stability or expressed concerns about the administrative workload associated with switching. Druedahl et al. [51] reported that industry stakeholders and European national medicines agency regulators believed that originator manufacturers had previously disseminated misinformation portraying biosimilars as inferior, which contributed to physician skepticism about their safety and efficacy. Notably, trust in the media was reported to be consistently low among US physicians across all specialties [52].

3.2.4.2 Involvement of Patient Organizations Patients in the US with autoimmune diseases emphasized a need for information and evidence to facilitate decision-making [49]. Experts from 24 different countries reported that one of the primary sources of information patients receive comes from patient organizations [29]. A common platform to share experiences and knowledge among patients was suggested. Patient representatives across Europe reported that "informa-

tion overshooting" should be avoided as excess information may generate patient concern [26]. In France, patients with rheumatoid arthritis or spondylarthritis reported obtaining biosimilar information predominantly from patient associations (50%), rheumatologists (39%), specialized magazines (30%), and the Internet (20%) [53]. While patient associations were a key source, rheumatologists were perceived as the most influential, with 78% of respondents ranking them highest compared to 64% for patient associations.

3.2.4.3 Nationwide/Statewide/Organization-Wide Campaigns or Modules New Zealand pharmacists wanted information from reputable sources such as the New Zealand Formulary (independent resource for health professionals), Best Practice Advocacy Centre New Zealand (independent educational organization), Pharmac (a government agency that decides which medicines are funded), Medsafe (New Zealand Medicines and Medical Devices Safety Authority), Health Navigator (health organization) or MIMS (pharmaceutical prescribing reference guide) [50]. During the transition to an adalimumab biosimilar, rheumatologists, rheumatology nurses, and pharmacists in New Zealand were not satisfied with information received from government agencies [15]. However, they were satisfied with the early timing of the information before the adalimumab transition took place.

Similarly, in Belgium, physician specialists and hospital pharmacists reported a lack of practical, non-industry-sponsored information and guiding principles in relation to switch management [37]. Prescribing rheumatologists, dermatologists, and gastroenterologists in the US reported they would like to receive best practice recommendations for non-medical switching included in the national disease treatment guidelines [49]. To enhance physician trust in biosimilars, industry experts and European national medicines agency regulators argued there is a need for medicines agencies to provide clear communication and justification in terms of biosimilar approval requirements, including whether biosimilar clinical trials for comparable efficacy are to be waived or reduced [51]. In addition, specialists in dermatology, diabetology, gastroenterology, and rheumatology in the UK reported that National Institute for Health and Care Excellence (NICE) guidance on biosimilars would likely increase their use of biosimilars [54].

Barbier et al. [27] reported that physicians, hospital pharmacists, nurses, patients, and regulators across Europe viewed a lack of stakeholder knowledge and understanding of regulatory biosimilar concepts as a major hurdle to biosimilar uptake. Regulators reported that actions have been taken to improve stakeholder knowledge about biosimilars, such as the development and distribution of information materials and the publication of biosimilar concept papers. In Belgium, physicians' lack of confidence in biosimilars can be explained by a knowledge gap, which could be due to an information gap. Manufacturers of original biologics invest large amounts of money in marketing and information catered towards physicians and patients. In contrast, manufacturers of biosimilars do not tend to make these efforts [28]. Pharmacists in Lebanon acknowledged a need for biosimilar programs in university curricula and continuing education programs [55].

4 Discussion

Barriers and facilitators to biosimilar adoption for treatment of immune-mediated inflammatory diseases were categorized under four key themes: regulatory and approval processes, healthcare system policies and incentives, infrastructure and logistics, and communication and education campaigns. Barriers included regulatory misalignment, unclear interchangeability guidance, short-term tenders, ethical concerns over prescriber incentives, administrative burdens, supply issues, limited patient support and training, and misinformation. Facilitators included centralized guidance, multi-winner tenders, gainsharing and fringe benefits, market share quotas, user-friendly devices, stable supply chains, early stakeholder engagement, transparent communication, and ongoing education. These findings offer a practical foundation for system-level strategies to support biosimilar adoption.

The findings support and extend previously recommended strategies for biosimilar adoption for treatment of immune-mediated inflammatory diseases. Existing recommendations emphasize the importance of early stakeholder education, inclusion of biosimilars in clinical treatment guidelines, and the promotion of user-friendly devices [56–60]. However, many of these strategies primarily target either the initial or post-adoption phase of implementation. Our review suggests that additional measures, such as the adoption of gainsharing models, offering fringe benefits rather than direct financial incentives, and the use of multi-winner tenders, may further improve brand changes. Incorporating these strategies alongside existing recommendations may help address barriers across all stages of the transition process by enhancing prescriber loyalty and promoting a more sustainable integration of biosimilars into clinical practice.

The findings highlight several facilitators that can be considered "low-hanging fruit"—relatively easy to implement without relying on major healthcare system reforms. Educational initiatives, such as continuing medical education for prescribers, incorporating biosimilar manufacturing and testing modules into medical curricula, training on new subcutaneous devices, and providing practical transition planning tools, can support knowledge and confidence among healthcare professionals. In addition, prescribing by INN

can be supported through electronic health record defaults or institutional guidelines [61]. This may also help pharmacists, who have reported high confidence in dispensing biosimilars in place of originators when products share the non-proprietary name [62]. Where possible, patient organizations, clinics, and pharmacy teams can also advocate for the procurement of biosimilars with citrate-free formulations, which may boost adherence and persistence [63]. Establishing departmental biosimilar market share targets or gainsharing incentive models (also known as benefit-sharing) can motivate uptake. However, there should be transparency in the outcomes of gainsharing programs for patients, with clear pathways for the redistribution of savings established [64]. Streamlining administrative processes like prior authorizations and maintaining access to patient support services can prevent disruptions during the brand change. Even relatively small adjustments, such as reducing tender frequency or avoiding unnecessary switching due to short-term contracts, may help maintain continuity of care. Together, these practical and locally driven strategies offer a scalable, responsive way to support biosimilar uptake.

Although the review did not directly compare healthcare systems, both Europe and the US show similar structures, with centralized product approval (EMA/FDA) but decisions about interchangeability and substitution left to national or state authorities [28, 33]. In the US, state-level regulations create a patchwork framework for pharmacist substitution of interchangeable biologics and rules vary in terms of whether substitution is mandatory or permissive, prescriber notification, patient consent, and pharmacist liability protection [65]. For example, in 2021, Sacks et al. [65] reported that physician notification of substitution is enacted by 45 states. A key difference between Europe and the US lies in the role of payers. In the US, insurance plans significantly influence biosimilar uptake. Stakeholders reported that switching is more common among patients with Medicaid or commercial insurance, particularly those enrolled in low-flexibility health plans [42]. In contrast, Medicare beneficiaries are less likely to switch, likely due to higher out-of-pocket costs under Medicare Part D reimbursement policies [66]. These differences underscore the importance of context-specific, system-tailored strategies to support biosimilar adoption.

It should also be noted that due to the substantial costs and regulatory complexity involved in biosimilar development, manufacturers have prioritized reference biologics with large market potential (typically those generating over USD 1 billion in annual sales) [67]. This concentration has further implications for market dynamics. For instance, it intensifies competition within a narrow set of therapeutic areas (e.g., in the case of adalimumab) [2, 67], while leaving other areas underserved. This uneven focus also shapes pricing and uptake patterns, as biosimilars tend to drive prices down where they are widely available, and adoption is generally quicker in areas like oncology, while uptake is slower in less competitive or niche therapeutic areas where fewer biosimilars exist [68, 69].

Similarly, policy uncertainty, such as around drug price regulation, creates additional challenges for biosimilar manufacturers. In the US, the recent Inflation Reduction Act enables Medicare to negotiate prices for certain high-cost drugs [70]. While this may help reduce spending, it creates uncertainty for biosimilar manufacturers, who may be less willing to invest in products if the financial returns are less predictable [71]. While the IRA includes some provisions to support biosimilars, such as delaying price negotiations if a biosimilar is expected to enter the market, its overall impact on investment remains unclear [70]. Similar challenges exist in other countries, where frequent changes to pricing policies, reimbursement rules, or single-winner tendering systems can make it difficult for manufacturers to plan long-term biosimilar strategies [72, 73].

Some originator manufacturers have also employed strategies that can delay or limit biosimilar uptake. Our review highlighted practices such as significant price cuts intended to deter biosimilar entry and delays in tender openings, sometimes linked to strategic contracts with originators to extend market exclusivity [32]. However, other tactics have also been reported in the literature, such as pay-for-delay agreements in which potential competitors are compensated to postpone market entry [74], patent evergreening to prolong exclusivity [75–77], and rebate bundling or contracting arrangements that financially disadvantage payers or providers adopting biosimilars [78]. Their limited visibility in our review likely reflects the perspectives of patients and healthcare professionals represented in some of the included studies, who may be less aware of upstream market dynamics, as well as the fact that many of these tactics occur before biosimilars reach the market. Policy interventions, including strengthened antitrust enforcement by agencies such as the US Federal Trade Commission, are essential to address these practices and promote a fair, competitive biosimilar landscape [78].

This scoping review has various limitations that should be considered. First, there are discrepancies between healthcare systems across different regions, which hinder the generalizability of the findings. It is acknowledged that this review includes limited discussion of regional regulatory processes. Consequently, the findings do not permit detailed cross-regional comparisons (e.g., between the FDA, EMA, and other agencies). Many studies also failed to adequately address the facilitators and barriers of biosimilar implementation, resulting in gaps in the data. For instance, several studies did not specify the exact biosimilar product used, leaving the methods of delivery unclear and making it difficult to draw definitive conclusions about the practical application of the findings.

Additionally, stakeholders in many studies were recruited from specific organizations, including drug manufacturers, raising concerns about potential biases that could influence the results. Early studies in this field may also not have sufficiently captured the barriers and facilitators to biosimilar uptake, especially given the rapid growth in biosimilar usage over the past decade. This gap in earlier research may limit the relevance of the conclusions drawn from those studies in the current context.

Looking forward, it is essential that future research acknowledges that healthcare systems are not one-size-fits-all. The challenges and opportunities for biosimilar adoption for treatment of immune-mediated inflammatory diseases vary widely across different settings, and a more nuanced, context-specific approach will be key to identifying the most effective strategies for adoption. There is also a pressing need for more studies that specifically address the implementation of facilitators, so that their effectiveness can be more comprehensively assessed. Furthermore, the development of global guidelines to standardize biosimilar practices, coupled with improved mechanisms for sharing information between countries, could advance the broader acceptance and implementation of biosimilars. Finally, overcoming persistent obstacles, such as resistance from manufacturers of bio-originator products, will be critical. Future research should aim to develop strategies that address these challenges and facilitate smoother transitions to biosimilar use in diverse healthcare environments.

5 Conclusions

This review examines systemic barriers and facilitators to biosimilar uptake for treatment of immune-mediated inflammatory diseases across healthcare settings globally. Four key domains (regulatory and approval processes, healthcare system policies and incentives, infrastructure and logistics, and communication and education campaigns) that impact the process of transitioning to biosimilars were identified. While there is variation between healthcare systems, the identification of practical, context-sensitive facilitators is crucial. Several facilitators, such as moving towards gainsharing incentive models and streamlining administrative processes, are actionable, low-burden strategies that can be adapted across diverse healthcare environments. Future research should focus on evaluating the real-world effectiveness of these strategies while also addressing gaps in reporting. Establishing global guidance and improving cross-country knowledge exchange will be essential for advancing the adoption of biosimilars.

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Declarations

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