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Physicians' perceptions on the uptake of biosimilars - A systematic literature review

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ABSTRACT

Objectives: Examine physicians' perceptions on the uptake of biosimilars

Design: Systematic literature review

Setting: Literature search in MedLine Ovid and Scopus databases at the end of 2018. Search resulted to 451 publications and after removal of duplicates, to 331 publications. Publications were examined based on the title, abstract and the entire text by two researchers. Twenty-one scientific original publications written in English that addressed physicians' perceptions on the uptake of biosimilars were selected for further analysis. Additionally, the references of selected articles were screened and two articles were handpicked and included in this review. Data of these 23 publications were extracted study-by-study basis. All publications were quality assessed by two researchers. In this review, higher emphasis was given to publications with high-assessed quality.

Results: Majority of selected studies were conducted in Europe and they commonly utilized short surveys. Physicians' familiarity of biosimilars varied: 49–76% were familiar with biosimilars and 2–25% did not know what biosimilars are. Measured knowledge appeared weaker compared to self-assessed knowledge. Physicians' perceptions towards biosimilars also varied: 54–94% were confident prescribing biosimilars, while 65–67% had concerns regarding these medicines. Physicians seem to prefer originator products to biosimilars and prescribe biosimilars mainly for biologic-naïve patients. Physicians consider cost savings and lower price in comparison to the originator biologic medicine as main advantages of biosimilars, while doubts often relate to safety, efficacy and immunogenicity. 64–95% of physicians have negative perceptions towards pharmacist-led substitution of biologic medicines.

Conclusions: Physicians' knowledge on and attitudes towards biosimilars vary. Although physicians had positive attitudes towards biosimilars, prescribing is limited, especially for patients that are already treated with biologic medicines. Perceptions towards the pharmacist-led substitution of biologic medicines are often negative. Education and national recommendations and policies for switching and substitution of biologic medicines are needed to support the uptake of biosimilars.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first systematic review conducted on the physicians' perceptions towards the uptake of biosimilars
- The literature search was conducted with the help of an experienced information specialist
- Publications selected for this review were quality evaluated by two researchers independently
- The evaluation protocol was compiled from four existing evaluation protocols

KEYWORDS
biosimilar, biologic medicine, physician, perception, systematic literature review

1 INTRODUCTION

Biologic medicines consist of one or multiple biologic active substances and are often manufactured through biotechnology[1-2]. Biologic medicines were first developed mainly for rare diseases, but have thereafter improved the treatment of many common diseases, such as diabetes, arthritis and psoriasis[1]. The flipside of this transformation are high costs of biologic medicines that have contributed to increased medical costs globally[3].

Biosimilars are biologic medicines highly similar to the originator biologic medicines with same standards on the quality, safety and efficacy of the products[2-4]. Biosimilars have no clinically meaningful differences to the existing reference product. Biosimilars are not regarded as generic medicines due to the complex manufacturing process and the natural variability between manufacturing batches of biologic medicines. The comparability of the product to the reference product has to be demonstrated, however, clinical trials are not required. As a result, biosimilars can be brought to the market with less expensive price in comparison to the originator biologic product. The uptake of biosimilars could lead to healthcare cost savings and better patient access to costly biologic therapies[5]. Until the end of 2018, 50 biosimilars have received marketing authorisation in Europe and 15 in the United States[6-7].

Regardless of the demonstrated comparability and their cost-saving potential, biosimilars have not fully penetrated the market of biologic medicines. The European Union holds 80% of global biosimilar market, but biosimilars constitute only 1% of total sales of biologic medicines[8-9]. It has been stated that the decisions of selecting biologic medicines are either policy driven or made by individual physicians, which has raised a need to assess the prescribing of biosimilars in a critical manner[10-11]. Physicians' attitudes towards and perceptions on the uptake of biosimilars have not been systematically reviewed, and published information on the topic is somewhat contradictory. The aim of this systematic literature review was to examine physicians' perceptions on the uptake of biosimilars.

2 MATERIAL AND METHODS

Literature search

A systematic literature search was conducted in MedLine Ovid and Scopus databases at the end of 2018. Selected databases provide a comprehensive selection of scientific publications from the disciplines of pharmacy and medicine. The search approach (**Appendix 1**) was set by the research group and the search was conducted by an information specialist.

The initial search resulted of 451 publications. After removal of duplicates (n=120), 331 publications remained. Publications were examined based on the title, abstract and the entire text by two researchers independently (KS and MM). Of the 331 publications, 151 were excluded based on the title, 148 based on the abstract and 11 based on the entire text. At each stage, researchers shared their views of the publications, discussed on possible differences on opinions and conducted a shared opinion based on the discussion. The inclusion and exclusion criteria of this systematic review are presented in **Table 1**. A total of 21 publications were selected for further analysis. Furthermore, the references of these 21 articles were screened and two articles that met the inclusion criteria were handpicked and included in this review, the final number of publications being 23. The flow chart on the review process is presented in **Figure 1**.

Table 1. Inclusion and exclusion criteria of publications of this systematic review.

Inclusion criteria	Exclusion criteria
• Scientific original publications	• Other than scientific original publications, such as conference papers, consensus papers, commentaries and letters to editors
• English language	• Other language than English
• Investigating physicians' perceptions on the uptake of biosimilars (physicians in particular or at least 45% of physicians among other healthcare professionals, although only physicians perceptions were taken into account in this review)	• Investigating other healthcare professionals' perceptions on the uptake of biosimilars or publications with less than 45% of physicians of all participants involved or in which the physicians' perceptions are not separated in the results of the study
• Publications on the physicians' perceptions on the automatic substitution of biologic medicines	• Publications on the physicians' perceptions on the automatic or generic substitution of other medicines than biologics

Quality assessment

Each of the 23 selected publications was concisely reviewed. Quality assessment was based on the protocol that was adapted from the protocols of Åkesson et al. (2006), Tong et al. (2007), Joanna Briggs Institute (2014) and Swedish Agency for Health Technology Assessment and Assessment of Social Services (2016)[12-15] (**Appendix 2**). Two researchers (KS and MM) conducted quality assessments individually and then compared their reviews. Differences in opinions (n=6) were discussed and final evaluation was set in consensus. In the Results section of this systematic review, publications with high-assessed quality are emphasized in comparison to the results of those with moderate or low assessed quality.

Data extraction and analysis

Following information of each publications were extracted to a table: general information (authors, year of publication, and country of publication), aims, methods and results. In regards to results, seven topics for data extraction were identified based on the topics discussed in the publications and on the discussion in the research group. These topics were: physicians' 1) self-rated knowledge of biosimilars, 2) measured knowledge on biosimilars, 3) information sources of biologic medicines, 4) attitudes towards and experienced advantages and disadvantages of biosimilars, 5) actions in the initiation of biosimilars for biologic-naïve patients, 6) actions in the switches between originators and biosimilars for patients already treated with biologic medicines and 7) thoughts on pharmacist-led substitution of biologic medicines. In the Results section of this systematic review, these seven topics are discussed within four broader themes: physicians' 1) self-rated and measured knowledge on biosimilars and information sources on biologic medicines, 2) attitudes towards and experienced advantages and disadvantages of biosimilars, 3) perceptions on the treatment initiations with biosimilars and on the switches between originator biologic medicines and biosimilars and 4) attitudes towards pharmacist-led substitution of biologic medicines.

3 RESULTS

Study characteristics

Physicians' perceptions on biosimilars have been studied mainly in European (n=15)[10, 16-28] and North American (n=4)[29-32] countries, apart from studies conducted both in Europe and North America (n=1)[33], Australia (n=1)[34], New Zealand (n=1)[35], Central and South America (n=1)[36] and in multiple African, European and Middle Eastern countries (n=1)[37] (**Table 2**). All publications were published between 2014 and 2019, but majority of them (n=19)[10, 16, 19-21, 23-32, 34-37] in 2017 or before. With the exception of a single publication[33], the data presented in the publications

Table 2. Summary of the 23 publications selected for this systematic review.

Reference (Country or region)	Aims and methods	Results						
		Self-rated knowledge	Measured knowledge	Information sources	Attitudes towards and experienced advantages and disadvantages of biosimilars	Initiation of biosimilars (biologic-naïve patients)	Switches between originators and biosimilars (patients already treated with biologicals)	Pharmacist-led substitution of biologic medicines
Akhmetov et al. 2015[16] (Ukraine)	Endocrinologists', oncologists', nephrologists', immunologists' and rheumatologists' awareness of biosimilars Short interviews with eight close-ended questions, including 6 Likert-type items (n=82), time of the study not reported	Low to medium levels (not reported more specifically) of biosimilar awareness on a 1-5 scale, where 1=low and 5=high) Endocrinologists and nephrologists had higher levels of awareness than other respondents	N/A	Peer-reviewed journal articles (n=35), internet (n=31), medical conferences (n=20), popular press (n=9), key-opinion leaders (n=3), drug manufacturers (n=2)	On a 1-5 scale, likelihood of prescribing biosimilars: 68% average (specific numbers not reported), 23% below average and 9% above average Majority (n not reported) are likely to try biosimilars in small batches, and then gradually move to larger groups of patients, endocrinologists and nephrologists showing the greatest interest Facilitators of prescribing: 39% cost advantage, 22% certification of safety by EMA or FDA, 22% certification of efficacy by EMA or FDA, 10% propitiousness of the Cabinet of Ministers and 7% trust towards European, American and Japanese biotech companies as importers Majority (n not reported) required 40-50% lower price for biosimilars than original biologics, endocrinologists typically accepting 20-30% discount in comparison to rheumatologists and oncologists that anticipated over 50% discount	N/A	N/A	N/A
Aladul et al. 2019[17] (the United Kingdom)	Knowledge and attitudes of healthcare professionals (n=150 dermatologists, diabetologists, gastroenterologists and rheumatologists) towards infliximab and insulin glargine biosimilars Web-based survey via selected medical associations between August 2016 and January 2017	80% were aware that biosimilars were available on their local formulary	76% correctly considered biosimilars as copies of originators	N/A	91% considered robust pharmacovigilance studies and 84% the costs as the most important influencer of their prescribing of biosimilars	22% had major concerns on the efficacy and 14% on the safety of biosimilars that prevented them of starting a biosimilar	50% had major concerns on the efficacy and 34% on the safety of biosimilars in the switches	N/A
Aladul et al. 2018[18] (the United Kingdom)	Perceptions of consultants with specialties of diabetes mellitus, ulcerative colitis, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis (n=10) towards biosimilar infliximab, etanercept and insulin glargine and potential barriers and facilitators to their prescribing Semi-structured interviews of purposive convenience sample of West Midlands hospital staff between June-November 2017	N/A	All interviewees expressed an understanding of the concept of biosimilars and believed biosimilars were copies of originators	Conferences, pharmaceutical industry representatives, scientific journals and colleagues	Majority of rheumatologists and diabetologists (n not reported) would prescribe the reference product if the prices of the reference product and the biosimilar are equal Gastroenterologists expressed more confidence and fewer concerns than other specialists, stating that indication extrapolation had previously been the major obstacle in the biosimilar uptake, but that it had been overcome Majority of rheumatologists (n not reported) had concerns on indication extrapolation, considering their patients are very sensitive with higher multimorbid risks. Some rheumatologists (n not reported) openly declared being mistrustful on biosimilars Facilitators of prescribing were information from societies, authorities and national registries. Barriers of prescribing were unexpected adverse effects or increase in side effects, patients' reluctance on using biosimilars, complicated, unsuitable or non-user-friendly administration device, unavailability of dose strengths in comparison to originators	Majority (n not reported) were content to initiate biosimilars Minority of rheumatologists and diabetologists (n not reported) felt under pressure to initiate new patients with biosimilars by their organization Two rheumatologists were happier to initiate biosimilars rather than switching	All gastroenterologists (n=7) and a minority of rheumatologists (n not reported) were content to switch patients from reference products to a biosimilar All those that were content with switching considered that patients should be given the choice between the products Majority of all physicians (n not reported) felt multiple switching based on cost reasons irrational	Majority (n not reported) has negative view on the pharmacist-led substitution of biologic medicines Minority (n not reported) considered that automatic substitution would be accepted in the next few years
Baji et al. 2016a[19] (Hungary)	Gastroenterologists' treatment preferences in ulcerative colitis Discrete choice experiment survey (in which prescribers are given hypothetical scenario and possible treatment options, and they are asked to choose the alternative they prefer[39]) in a Hungarian professional society meeting in 2014 (n=51)	N/A	N/A	N/A	20% had no concerns on biosimilars, 67% had some concerns on efficacy and/or safety and 12% did not support the use of biosimilars due to the lack of RCT evidence	84% of all physicians and 80% of those who had some concerns (67%) chose biosimilar in at least one choice set The most important attribute driving the choice: stopping rule (whether treatment after 12 months is reimbursed) Estimated probability of choosing the originator over biosimilar in the present reimbursement situation: 48%. Probability of choosing the biosimilars with all the benefits offered over the originator in the present situation: 85% versus 15%	61% of all and 53% of those who were concerned chose biosimilar in at least one of the choice sets The most important attribute driving the choice: stopping rule Estimated probability of choosing the originator over biosimilar in the present reimbursement situation: 71%. Probability of choosing the biosimilars with all the benefits offered over the originator in the present situation: 63% versus 37%	N/A

Baji et al. 2016b[20] (Hungary)	Gastroenterologists' treatment preferences in Crohn's disease Discrete choice experiment survey (in which prescribers are given hypothetical scenario and possible treatment options, and they are asked to choose the alternative they prefer[39]) in a Hungarian professional society meeting in 2014 (n=51)	N/A	N/A	N/A	20% had no concerns on biosimilars, 65% had some concerns on efficacy and/or safety and 12% did not support the use of biosimilars due to the lack of RCT evidence Four clinicians were classified to "No biosimilar" attitude group, 19 to the "Biosimilar to new patients only" group and 27 to the "Biosimilar" group (one clinician was excluded from the analysis)	Men, senior consultants, working in inflammatory bowel disease centre and treating more patients were more likely to consider biosimilars for biologic-naïve patients only Estimated probability of choosing the originator over biosimilar, when no benefits are offered for using the biosimilar: 60%. Probability of choosing the biosimilar with all kinds of benefits over the originator: 89% versus 11% The most important attribute driving the choice: continuity of medicine supply	Estimated probability of choosing the originator over biosimilar, when no benefits are offered for using the biosimilar: 74%. Probability of choosing the biosimilar with all kinds of benefits over the originator: 44% versus 56% The most important determinant of choice: type of the treatment	N/A
Barsell et al. 2017[29] (USA)	Dermatologists' knowledge and perceptions of biosimilars, whether a practice gap exists and to study misconception and barriers to biosimilar usage Web survey of 14 multiple-choice questions for the members of five state dermatologic societies and National Psoriasis Foundation in 2015 (n=97)	62% responded having basic understanding of biosimilars, 27% complete understanding and 11% that they have never heard of biosimilars	37% were aware that biosimilars are highly similar to the reference product, 26% described biosimilar as "generic", 27% described them as same bio-drug with equal bioequivalence and 10% said they did not know the definition. Those with complete understanding (27%), 21% incorrectly described biosimilar as "generic"	35% self-study, 25% scientific publications, 17% conferences and seminars, 3% biosimilar company-sponsored events and 20% other	Advantages: 71% low price to patients, 68% easier access to treatment and 65% low price to payers. Disadvantages: 71% efficacy, 66% potential switch to biosimilar without physicians' knowledge, 66% safety and 63% immunogenicity. 8% believed there were no advantages Convincing physicians of interchangeability: 44% extensive phase I, II and III studies, 37% valid longitudinal data from patient registries, 37% same level of testing (not specified more thoroughly) than generic medicines, 36% evidence of pharmacokinetic and pharmacodynamic equivalence	25% definitely or highly likely to prescribe a biosimilar 38% will try it on very selected patients	N/A	88% believed that there will be a political change resulting to pharmacist-led substitution without consulting physicians in the future 76% very important and 18% somewhat important to have control over whether patients receive originator or biosimilar
Beck et al. 2016[21] (France)	Knowledge, experience and opinions related to biosimilars and to identify expectations, barriers and possible options to promote prescription Web survey of 22 questions for nearly 500 rheumatologists in 2015 (n=116)	55%/3% considered they had little/no knowledge of biosimilars 5% felt very well-informed Hospital-based rheumatologists were likely to be more familiar with biosimilars compared to office-based rheumatologists 98% had at least one question about biosimilars	85% thought biosimilars are similar to reference products that had gone off-patent; 85% considered biosimilars have no meaningful differences in quality, 80% in safety and 90% in efficacy; 65% thought that the assessment of biosimilarity requires more comprehensive data than generic drugs; and 46% believed that biosimilar marketing authorisation is granted on the sole investigation of pharmacokinetic bioequivalence	84% self-study and scientific publications, 76% pharmaceutical companies, 72% continuous training, 54% physician colleagues and 19% pharmacist colleagues	44% agree and 10% strongly agree being in favour of implementation of biosimilars Positive factors: 90% healthcare cost savings, 61% releasing of resources allowing treating additional patients, 49% positive impact on patients' access to innovative medicines and 46% health policy-makers incentives. Barriers: 67% indication extrapolation of efficacy and safety, 66% lack of information about tolerability, 59% risk of increasing patients' concerns, 57% lack of clinical trials and 55% patients' wishes to be treated with the originator	7% had already prescribed biosimilars mentioned in the survey 89% considered it was conceivable to start a treatment for biologic-naïve patients	25% could envision a switch	58% strongly disagree and 23% disagree of approving substitution by a pharmacist
Chapman et al. 2018[22] (the United Kingdom)	Healthcare professionals' knowledge and attitudes towards infliximab and insulin glargine biosimilars and factors influencing their prescribing and compare healthcare professionals' attitudes with the utilisation of these biosimilars in hospitals Web-based survey of 11 questions for societies of dermatology, diabetology, gastroenterology and rheumatology in 2016-2017 and drug utilisation analysis from DEFINE database in 2015-2016 (n=234). Other stakeholders apart from physicians are not addressed in this review	N/A	72% correctly thought biosimilars are similar copies of biologic medicines, 18% thought biosimilars are generic biologic medicines, 3% counterfeit medicines, 3% had heard of them but did not know what they were, 3% had never heard of them and 1% new biological medicines 75% knew biosimilars were available on their local formulary	N/A	Gastroenterologists were most frequent prescribers of biosimilars (prescribing every day or week), followed by rheumatologists, diabetologists and dermatologists The dominant consideration: cost saving Increasing the use of biosimilars: regulatory guidance and robust pharmacovigilance studies, local policy, potential cost saving to organisation (whether or not savings were invested in the prescribers' department) and robust cost-effectiveness data of biosimilar vs. originator	95% and 90% of gastroenterologists, 92% of rheumatologists, 79% of dermatologists and 75% of diabetologists had no or minor concerns on safety 90% of gastroenterologists, 88% of rheumatologists, 74% of dermatologists and 68% of diabetologists had no or minor concerns on efficacy	95% of gastroenterologists, 53% of rheumatologists, 78% of dermatologists and 69% of diabetologists had no or minor concerns on safety 93% of gastroenterologists, 55% of rheumatologists, 79% of dermatologists and 65% of diabetologists had no or minor concerns on efficacy	N/A
Cohen et al. 2016[30] (USA)	Dermatologists', gastroenterologists', haematologist-oncologists', medical oncologists', nephrologists' and rheumatologists' awareness, knowledge, and	N/A	92% of dermatologists, 90% of gastroenterologists, 83% of rheumatologists, 74%	88% scientific journals, 73% FDA and 64% physician peers. Trust to media was less than 5%	Generally positive attitudes towards biosimilars. Dermatologists and rheumatologists appear less enthusiastic	N/A	91% open to switching patients to a biosimilar	N/A

	perceptions of biosimilars over time (survey will be repeated in 2-3 years) Survey of 19 questions in 2015-2016 (n=1201)		of nephrologists, 69% of haematologist-oncologists and 63% of medical oncologists were aware which of the listed medicines in their specialty were biologic 56% of rheumatologists, 33% of gastroenterologists, 31% of dermatologists, 15% of nephrologists, 9% of medical-oncologists and 3% of haematologist-oncologists incorrectly reported there are no biosimilars available		62% considered the biosimilar will have equivalent efficacy as its originator and 57% that the biosimilar will be at least as safe as the originator 58% had concerns on patient compliance and access to treatments options with originators Positive factors: increased access and utilization of biologic medicines, expanded treatment options and provided savings for the healthcare system			
Danese et al. 2016[23] (Europe, countries not reported)	Evolution on thinking about biosimilars one year after they had become available in the EU. Comparison to the survey published by Danese et al. 2014[24] Web survey with 14 multiple-choice questions for members of European Crohn's and Colitis Organization in 2015 (n=118)	56% judged that educational activities that they were exposed to was fair and adequate, while 16% found it unnecessary	N/A	More information was hoped from 75% medical societies, 52% multispecialty safety registries, 47% health institutions and 26% guidelines	29% totally confident, 18% very confident and 34% confident enough (5%, 8% and 26% in 2013) to prescribe a biosimilar Main advantage: 92% (90% in 2013) cost-sparing. Main issue: 42% the lack of data from clinical trials for all indications 27% (67% in 2013) consider biosimilars have higher immunogenicity compared to the originator and 17% (43% in 2013) different action than the originator 51% (24% in 2013) thought biosimilar should be approved for all the indications of the originator	N/A	44% (6% in 2013) would switch a patient with remission	89% (85% in 2013) disagreed with automatic substitution by a pharmacist 13% support substitution for new prescriptions and 13% for all patients
Danese et al. 2014[24] (Europe, countries not reported)	Awareness of and readiness to use biosimilars Web survey of 15 questions for 1,000 randomly selected European Crohn's and Colitis Organization members in 2013 (n=307)	N/A	70% were aware that biosimilar is a similar copy, but not equal to the originator, 19% responded that it is a copy of biological agent, identical to the originator, like a generic	Preferred information: 81% multi-specialty international safety registries to monitor safety and effectiveness, 78% health institutions on the development of rules on the use of biosimilars, 66% medical societies, 61% data regarding the registration process for biosimilars and 57% multispecialty practice guidelines	6% thought that the originator and biosimilar were interchangeable The main advantage: cost-sparing (89%). The main issue: different immunogenicity pattern than the originator (67%) 50% agreed biosimilars can significantly reduce healthcare costs, 27% expected them only having a marginal impact, 6% expected additional costs of introduction, regulation and pharmacovigilance to offset any potential savings 24% agreed that the tested biosimilar could be approved for all indications of the originator in terms of safety and efficacy, 19% for all rheumatologic indications, 14% for the specific indication only, 3% stated that all biosimilars could be approved for all indications of the originator and 39% disagreed with all of the above	61% felt little or no confident in using biosimilars in their everyday clinical practice, 26% confident enough, 8% very confident, and 5% totally confident	28% would consider replacing originator with a biosimilar	64% against the substitution by pharmacist 18% would agree only for new patients
Farhat et al. 2016[37] (Algeria, Belgium, Egypt, Iran, Iraq, Italy, Jordan, Lebanon, Sudan and Syria)	Parameters on the acceptance and future prescription of biosimilars and worldwide situation focusing mainly on the EU and US laws, regulations and legislative pathways, pricing and challenging market access Survey for over 150 healthcare professional in the conference meeting in 2015 (n=117 health care professionals responded, of which most were physicians; exact number of physicians who responded not reported). Other stakeholders apart from physicians are not addressed in this review	N/A	66% knew what biosimilars were, 12% did not know and 22% had not answered the question. Of those who knew (66%), 62% considered biosimilars bioequivalent to originator and have all preclinical and clinical trials equal to the originator 63% agreed that biosimilars are already marketed in the Arab and Middle Eastern markets, while 45% agreed that they are manufactured in the same region	N/A	Drivers for prescribing: 69% FDA or EMA approval, 65% lower price of bioequivalence in comparison to the originator, 48% bio-efficacy, 42% safety and 31% good manufacturing practices and high reputation of the manufacturer. 5% think biosimilars don't have advantages 35% considered the cost of treatment should not overcome its effectiveness or safety/tolerance 26% thought lower prices were good news as patients will be treated with biologics 27% consider biosimilars would bring cost savings 49% trust companies highly experienced in manufacturing small-molecule generic drugs and 55% companies with prior experience in manufacturing biologics as biosimilar producers	41% prescribe biosimilars while 33% don't (note that respondents were also other than physicians)	N/A	N/A
Felix et al. 2014[31] (USA)	Challenges and opportunities of market uptake of biosimilars from the perspectives of physicians and payers Survey for physicians that had written about or were familiar with biosimilars based on literature	N/A	N/A	N/A	Almost all physicians (n not reported) believed that if biosimilar was approved by FDA it will perform similarly to the originator with regard to safety and efficacy Influences of decision making: efficacy and safety, out-of-pocket costs to the patient, price of treatment and immunogenicity	Four physicians are somewhat likely, six very likely and three not likely to prescribe a biosimilar to a new patient	31%/61% (n not reported) say they are somewhat likely/very likely to switch an existing patient from originator to biosimilar	N/A

	review of Medline-indexed publications (n=14). Other stakeholders apart from physicians are not addressed in this review				50% (n not reported) consider it is very important that there are proven chemical and pharmacokinetic similarities between originators and biosimilars Roughly half (n not reported) consider payer and cost considerations very important			
Gewanter & Reilly 2014[36] (Argentina, Brazil, Colombia and Mexico)	Understanding of biosimilars, how they use them and their concerns for the future Web-based survey for 6650 prescribers from global market research panel (n=399)	35% did not consider themselves familiar with biosimilars, meaning they could not define them or had never heard of them	49% were aware of differences between biologicals, biosimilars and non-comparable biologicals. 30% were unaware that clinical trials for single indication lead to approval for multiple indications	71% seminars and conferences, 55% self-study, 32% education from biosimilar companies, 18% clinical trial participation and 4% other means 37% would like to learn from pharmaceutical companies	88% prescribe biologicals	50% said they believed if two biological medicines had the same non-proprietary scientific name, patient could receive either product and have the same result	44% said they believed if two biological medicines had the same non-proprietary scientific name, patient could be safely switched during a course of treatment, and the patient would have the same result 64% would not be comfortable switching for cost reasons rather medical reasons	N/A
Grabowski et al. 2015[32] (Canada)	Gaps in knowledge and attitudes towards biosimilars of rheumatologists Web-based survey of 29 questions for 369 members of Canadian Rheumatology Association in February 2014 (n=81)	31% indicated themselves being familiar or very familiar with biosimilars Those with greater than 20 years of practice were significantly more likely to indicate themselves familiar or very familiar than those with 20 or less years of practice	66% considered biosimilars essentially same as generic drugs 38% were aware of Health Canada's guidance on clinical requirement for biosimilar approval	N/A	94% generally comfortable prescribing biologic medicines to their patients 31% comfortable prescribing biosimilars to their patients if biosimilar was currently available 29% declined until their colleagues recommend it 42% indicated a 30% price reduction, and a third a ≥50% price reduction being reasonable before payers mandated the use of biosimilars over brand name biologics 54% disagreed or strongly disagreed, 32% agreed or strongly agreed and 14% were neutral using biosimilars with extrapolated indications 49% not confident, 19% confident or very confident, and a third neutral on the long-term sustainability profile of the biosimilar with 30 weeks of head-to-head clinical trial	59% consider offering biosimilars, if biosimilar demonstrates that it is comparable to the brand name drug 72% unlikely or very unlikely, 11% likely or very likely and 16% neutral to offer a biosimilar, when biologic-naïve patient is an ideal candidate, where cost is not an issue Greater familiarity with established brand name drugs and uncertainty over the long-term safety of biosimilars were often cited among those unlikely or very unlikely offering biosimilars 54% did not typically prescribe a biosimilar, were likely or very likely to offer a biosimilar, when the provincial payer or insurance company mandated using a biosimilar	7.5% consider switching, if biosimilar demonstrates that it is comparable to the brand name drug	88% concerned or very concerned if a pharmacist had the ability to substitute a biologic drug for a biosimilar without the physician's approval
Hemmington et al. 2017[35] (New Zealand)	Perceptions and attitudes towards efficacy, safety and manufacturing of biosimilars, factors associated with positive attitudes, indication extrapolation and switching, and circumstances in which physicians would be reluctant to prescribe biosimilars E-mail survey for 327 physicians in medical specialist society (n=110)	76% reported being familiar and having basic understanding and 13% very familiar and complete understanding of biosimilars, 9% had heard of biosimilars, but could not define them, and 2% had never heard of biosimilars	N/A	N/A	70% very or somewhat confident of the efficacy of biosimilars Less than 20% had negative views Situations when biosimilars were not prescribed: 32% lack of clinical data, 17% evidence of adverse effects or lack of efficacy, 15% patients do well with current treatment and 6% patients have complex medical history 47% very confident or somewhat confident, 32% not confident and the remainder undecided in indication extrapolation	71% would prescribe biosimilars for all or some clinical conditions meeting the relevant criteria, 10% would do this for only few or no clinical situations	51% confident and 28% not very confident or not at all confident to switch patients	N/A
Leonard et al. 2019[33] (Europe and USA)	Healthcare provider knowledge, perceptions, and prescribing behaviours of biosimilars and, need for clinician-directed biosimilar education Systematic literature review in PubMed, Embase, and Cochrane Library databases from January 2014 to March 2018 (n=20 publications). Other stakeholders apart from physicians are not addressed in this review	Physicians often described having only little knowledge on biosimilars The shares of described having a good knowledge were low. Those that described having a high level of familiarity with biosimilars, often incorrectly defined biosimilarity, reflecting the discrepancy between claimed and actual knowledge	Majority of physicians (in different studies that were included in the systematic review) had incomplete or basic understanding of biosimilars Familiarity of biosimilars appeared greater in hospital-based clinicians than office-based clinicians	Self-study, peer-reviewed journals, professional guidelines, discussion with physician and pharmacist colleagues, manufacturer promotional material, educational programs and conference/ seminar attendance	Physicians were hesitant about the safety, efficacy and indication extrapolation of biosimilars. Safety concerns often related to immunogenicity and indication extrapolation concerns to the lack of clinical trials. Years of practice did not significantly effect on prescribing behaviour	Biosimilars were largely considered second-line therapies for biologic-naïve patients Some physicians would limit the use of biosimilars to a small patient population first	N/A	Physicians were mainly hesitant about pharmacy-driven substitution of biologic medicines Some studies reported that physicians were unaware that interchangeability could enable pharmacist-led substitution There were only some studies reporting positive attitudes towards pharmacy-led substitution
O'Callaghan et al. 2017[10] (Ireland)	Medical specialists', general practitioners' and community pharmacists awareness of and attitudes to biosimilars	44% of medical specialists and 5% of general practitioners very familiar with biosimilars, 41% and	25% of medical specialists and 18% of general practitioners considered biosimilars	Medical specialists (n=101, not all answered this question): 72% guidelines from professional societies,	59% of those aware of biosimilars in their therapeutic area (n=73) prescribed biosimilars, while 40% didn't Concerns: 81% efficacy in extrapolated indications, 81% immunogenicity, 79% efficacy, 78% safety, 73% quality and 62% traceability	67% of medical specialists that prescribed biosimilars (n=43) would most likely prescribe a biosimilar for treatment initiation	28% of medical specialists that prescribed biosimilars (n=43) would be likely to switch from originator to biosimilar	<5% of medical specialists would consider pharmacist-led substitution appropriate

	E-mail-survey of 14-20 questions for 2917 physicians in national professional societies in 2016 (n=253 analysed answers from general practitioners and n=102 from medical specialists). Other stakeholders apart from physicians are not addressed in this review	35% familiar , and 6% and 25% had never heard the term "biosimilar"	the same as generic medicines 31% of medical specialists incorrectly agreed that biological medicines sharing the same international non-proprietary name were "structurally identical"	68% published literature and 63% educational events GPs (n=247, not all answered this question): 58% national or hospital formularies				49% consider decisions should be taken by the prescriber on treatment initiation and 61% during treatment course. 43% consider decisions should be agreed with clinician in advance on treatment initiation and 35% during treatment course 84% think notifications for physician very important or critical in treatment initiation and 90% during treatment course
O'Dolinar & Reilly 2014[25] (France, Germany, Italy, Spain and the United Kingdom)	Nephrologists', rheumatologists', dermatologists', neurologists', endocrinologists' and oncologists' attitudes on biosimilar naming, substitution, and knowledge, sources of information and need for further education on biosimilars Web-based 15-minutes short survey for 4,324 global physician market research panel of at the last quarter of 2013. 470 prescribers (20% of each five countries) completed the survey	46% responded having basic understanding, 43% complete understanding, 11% could not define biosimilars and 1% had never heard of biosimilars 53% incorrectly thought biosimilar and originator were structurally identical and 37% incorrectly believed biosimilars are clinically tested for all indications	N/A	47% conferences and seminars, 35% self-study, 11% studies sponsored by biosimilar companies and 6% equally studies sponsored by innovator companies, clinical trial participation and other routes	48% said it was very important, 24% critically important, 23% somewhat important, 4% slightly important and 1% not important to have a sole authority to select the medicine	47% considered that products with the same non-proprietary name could be safely given to a patient with same results, 40% didn't think that way	45% think patients can't be switched between the products with same non-proprietary names, 39% believed patients could be switched safely and effectively	62% not acceptable, 35% acceptable and 3% totally acceptable on pharmacist-led substitution 47% very important, 30% critical, 6% slightly important and 1% not important to receive a notification if the pharmacist had dispensed other than prescribed biologic medicine during a repeated treatment
van Overbeeke et al. 2017[26] (Belgium)	Knowledge and perceptions of patients and physicians with regard to originators and biosimilars and differences in perceptions and the factors influencing their preferences Web survey of multiple-choice and open-ended questions for all 232 Belgian rheumatologists in 2016 (n=41 responded). Other stakeholders apart from physicians are not addressed in this review	95% considered biosimilars are similar, but not identical	90% were able to share the most complete definition of a biosimilar	N/A	7% had prescribed biosimilars. 73% preferred the originator when the prices were equal and 38% when originator was more expensive. When prices were equal, none preferred biosimilar. 93% considered price, 63% safety, 61% quality and 61% efficacy as sources of differences between originators and biosimilars 33% considered biosimilars and originators interchangeable if biosimilarity is proven in the same indication and 38% if in indications where the medicine works via the same biological mechanism. 28% considered that biosimilars and originators were never interchangeable 56% think extrapolation could only be performed if efficacy and safety is proven to be similar in one of the indications and if the medicine works via the same mechanism in the other indications. 39% stated the indications should never be extrapolated Positive influencers: clinical trials with positive results and clinical data in the respective indication. Negative influencers: less studied than the originator and no clinical trials in the respective indication	8% would not prescribe a biosimilar and 60% would only prescribe a biosimilar to biologic-naïve patients.	N/A	N/A
Reilly & Murby 2017[34] (Australia)	Opinions on the naming of biologicals and biosimilars, how the use of these medicines is recorded and their views on substitution of, familiarity with, knowledge of, attitudes to and beliefs in biosimilars Web-based survey for prescribers recruited from a global, commercial database of health care professional in 2016 (n=451, of which 160 completed the survey)	21% considered themselves very familiar and having complete understanding of biosimilars, 73% basic understanding and 6% could not define them	50% thought biosimilars go through the same regulatory process as original biologics 70% knew biosimilars could be approved for all or for some indications of the originator	46% published literature, 28% colleagues, 27% information from Pharmaceutical Benefits Advisory Committee, 24% product information label, 19% information from Therapeutic Goods Administration, 18% sales presentative, 13% hospital formulary 43% never used published literature	N/A	16% would be comfortable prescribing a biosimilar that was approved for several indications based on clinical trials in only one indication, 11% would not feel comfortable and 73% had some concerns on this	N/A	54% very and 36% critically important to have sole authority to decide of which biological was dispensed Evidence required for pharmacist-led substitution: 53% clinical trial data of no safety of efficacy risks in switching, 53% clinical trial data of no safety of efficacy risks after multiple switches, 27% in-market experience, 24% observational data and 6% no evidence would be sufficient
Sullivan et al. 2017[27] (Germany)	Motivators of prescribing biosimilars, preferences matching actual prescribing behaviour and patient	N/A	N/A	N/A	Biosimilars account for 12-13% of all biologic therapies the respondents prescribe	88% would prefer to prescribe originator to biosimilar as 1st line therapy	N/A	N/A

	acceptance, satisfaction and concerns on biosimilars and how these relate to the treatment with originators or biosimilars Real world, cross-sectional study (in which physicians filled a survey form and reported their prescribing, and recruited patients that also filled a questionnaire form to provide information on how reported prescribing was occurred in practice) in 2015-2016 (n=25). Other stakeholders apart from physicians are not addressed in this review Based on their response, 11 physicians were assigned to investigative (primarily concerned with symptom improvement and disease modification), 7 to conservative (primarily concerned with safety) and 7 to other (influenced primarily by other factors)				Reasons to prescribe: desire to get experience with the new product (89% of investigative, 100% of conservative and 57% of other), being convinced of equivalent efficacy compared to originators (44%, 67% and 43%), lower cost (44%, 83% and 71%), believing that is economic prescribing (44%, 83% and 57%) and believing that using biosimilars makes savings which can be used elsewhere (22%, 67% and 29%)			
Waller et al. 2017[28] (Germany)	Motivators of prescribing biosimilars, preferences matching actual prescribing behaviour, and patient acceptance, satisfaction and concerns on biosimilars and how these relate to the treatment with originators or biosimilars Real world, cross-sectional study (in which physicians filled a survey form and reported their prescribing, and recruited patients that also filled a questionnaire form to provide information on how reported prescribing was occurred in practice) in 2015-2016 (n=50). Other stakeholders apart from physicians are not addressed in this review Based on their response, 23 physicians were assigned to investigative (primarily concerned with symptom improvement and disease modification), 17 to conservative (primarily concerned with safety) and 10 to other (influenced primarily by other factors)	N/A	N/A	N/A	Biosimilars constitute less than 10% of the biologic therapies the respondents prescribed Reasons to prescribe: desire to get experience with the new product (86% of investigative, 65% of conservative and 50% of other), being convinced of equivalent efficacy compared to originators (64%, 65% and 50%) and lower costs (64%, 71% and 88%)	>95% would prefer to prescribe originator to biosimilar as 1st line therapy	N/A	N/A

were collected between 2013 and 2017. Most of the 23 selected publications utilized surveys, typically web-based questionnaires with 11–22 questions, or fully structured short interviews (n=16)[10, 16-17, 21-24, 25-26, 29-30, 32, 34-37]. In addition there was a qualitative interview study[18] and real-world cross-sectional studies (n=2)[27-28], in which physicians filled a survey form and reported their prescribing and after, recruited patients that also filled a questionnaire form to provide information on how reported prescribing actualized in practice. There were also discrete choice method surveys (n=2)[19-20], in which prescribers were given a hypothetical scenario and possible treatment options, and they were asked to choose the alternative they prefer[38]. Furthermore, one systematic literature review on healthcare professionals' perceptions on biosimilars[33], and one literature review with survey on the market uptake of biosimilars[31], have been conducted.

Quality assessment

Of 23 selected publications, nine[10, 17, 19-20, 22, 26, 32-33, 35] were evaluated to be high, five[18, 21, 27-29] to be moderate and nine[16, 23-25, 30-31, 34, 36-37] to be low in quality based on criteria used in this review (**Table 3**). Publications evaluated to be high in quality often included well-described and logically presented methods and results sections and a critical discussion section, of which those evaluated to be moderate or low quality typically lacked. In general, the quality assessment revealed that there is a lack of valid instruments and studies utilizing qualitative research methods.

Self-rated and measured knowledge on biosimilars and sources of information (n=18)

There is variation on the physicians' self-rated knowledge on biosimilars (**Table 2**). In individual studies, physicians consider they have at least a basic understanding of the topic: 5–44% of the physicians reported that they feel very familiar and 49–76% that they feel familiar with biosimilars[10, 23, 25-26, 29, 32, 34-36]. In these studies 2–25% of the physicians reported that they do not know what biosimilars are. In individual studies, physicians with more years of practice and those with specialisation consider themselves more familiar with biosimilars in comparison to less experienced colleagues and general practitioners[10, 21, 32]. On the contrary, a systematic literature review suggests that physicians often think that they only have little knowledge on the topic and that years of practice do not significantly effect on prescribing behaviour [33].

Although physicians self-rate that they generally feel familiar with biosimilars, the measured knowledge on the topic appears weaker (**Table 2**). 18–66% of the physicians incorrectly described biosimilars as generic medicines and 31–72% as structurally identical to originator medicines[10, 21-22, 24, 30, 32, 34, 36-37]. However, in three studies, 76–100% of physicians were able to share the complete definition of a biosimilar correctly[17-18, 26].

Physicians use several information sources on biologic medicines, such as scientific publications (25–84%), self-study (35–84%), pharmaceutical companies (32–76%), guidelines from professional societies (26–75%), educational events and conferences (17–71%), published literature (46–68%), physician colleagues (28–54%), safety registries (52%) and pharmacist colleagues (19%)[10, 16, 18, 21, 23-25, 29-30, 33-34, 36] (**Table 2**). According to a single study and a systematic literature review, information sources may vary according to the educational background of physicians, as the most common information source were the guidelines from professional societies for medical specialists and the national or hospital formularies for general practitioners[10, 33].

Attitudes towards and experienced advantages and disadvantages of biosimilars (n=22)

Reporting on the physicians' attitudes towards biosimilars seems contradictory[10, 19-24, 26-32, 35-37] (**Table 2**). Some studies show that 65–67% of physicians have concerns regarding biosimilars[19-20], while others report that 54–94% of physicians feel somewhat or very confident prescribing biosimilars[10, 21, 23, 32, 35]. Regardless, positive attitude towards biosimilars does not automatically translate into prescribing, as physicians seem to prefer originator

Table 3. Summary of the quality evaluation of the 23 publications selected for this systematic review.

Reference	Main strengths	Main limitations	Quality according to the quality assessment protocol
Aladul et al. 2019[17]	Results logically and clearly displayed	Details of the questionnaire form were not available, discussion on methodology partly lacking	High
Baji et al. 2016a[19]	Well-described and logically presented methodology, results and discussion	Ethical discussion lacking	High
Baji et al. 2016b[20]	Well-described and logically presented methodology, results and discussion	Critical and ethical discussion partly lacking	High
Chapman et al. 2018[22]	Mainly well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
Grabowski et al. 2015[32]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High*
Hemmington et al. 2017[35]	Well-described and logically presented methodology, results and discussion	Details of the questionnaire form were not available, more in-depth information could have been collected by a qualitative study	High
Leonard et al. 2019[33]	Systematic approach with well-described methodology, results and discussion	Quality assessment of publications selected for systematic review is lacking, data not extracted study by study basis, no two reviewers in all steps of the systematic literature review process	High
O'Callaghan et al. 2017[10]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
van Overbeeke et al. 2017[26]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
Aladul et al. 2018[18]	Semi-structured interviews provide a more in-depth view on the perceptions of healthcare professional in comparison to short surveys	Exact numbers of respondents which certain opinion (n) not always reported, low number of representatives per each professional group	Moderate*
Barsell et al. 2017[29]	Well-presented results and discussion	Details of the questionnaire form were not available, description of methodology lacking, e.g. dropout not described, ethical discussion lacking	Moderate
Beck et al. 2016[21]	Well-presented results and discussion	Details of the questionnaire form were not available, validity of the instrument unclear, as more in-depth information could have been collected by a qualitative study, dropout not described accurately	Moderate*
Sullivan et al. 2017[27]	Results clearly presented	Dropout not described accurately, some inconsistencies in the presentation of methodology and discussion	Moderate*
Waller et al. 2017[28]	Well-presented results and discussion	Some inconsistencies in the presentation of methodology, e.g. sample selection and dropout	Moderate*
Akhmetov et al. 2015[16]	Explicit aims	Clear presentation of results lacking, critical and ethical discussion lacking	Low
Cohen et al. 2016[30]	Mainly well-presented results and discussion	Details of the questionnaire form were not available, description of methodology lacking, ethical discussion lacking	Low
Danese et al. 2016[23]	Results clearly presented	Details of the questionnaire form were not available, critical and ethical discussion partly lacking, description of methodology partly lacking	Low
Danese et al. 2014[24]	Results clearly presented	Statistical analyses lacking, critical and ethical discussion lacking, description of methodology partly lacking, for example the number of invited members not mentioned	Low
Farhat et al. 2016[37]	Mainly logically presented methodology	Aim is not explicitly presented, number of physicians who responded not reported, results presented in table format only, critical discussion lacking	Low*
Felix et al. 2014[31]	Explicit aims	Strategic sample selection, details of the questionnaire form were not available, exact numbers of respondents which certain opinion (n) not always reported, description of used statistical methods and data analysis lacking, inconsistency in the description of results	Low
Gewanter & Reilly 2014[36]	Explicit aims	Respondents from market research panel resulting that respondents work in disciplines in which don't necessarily involve biosimilars, such as psychiatry, description of used statistical methods and data analysis lacking, critical and ethical discussion lacking	Low
O'Dolinar & Reilly 2014[25]	Explicit aims	Intentional sample selection, clear presentation of results lacking, critical and ethical discussion lacking	Low
Reilly & Murby 2017[34]	Explicit aims	Description of data collection partly lacking, description of used statistical methods and data analysis lacking	Low

* Differences in opinions of which quality grade each publication was given, set in consensus

products to biosimilars[19, 26, 32]. Studies indicate that there might be differences in attitudes towards biosimilars between specialties: gastroenterologists seem frequent prescribers of biosimilars, while dermatologists and rheumatologists seem less enthusiastic[18, 22, 30].

The main experienced advantages of biosimilars are cost savings[17, 21-24, 29], lower price in comparison to the originator biologic medicine[29, 37] and physicians' willingness to try new treatments[27-28] (**Table 2**). Additionally, in single studies, robust pharmacovigilance studies[17], easier access to treatment for patients[29], and approval of the European Medicines Agency or the Food and Drug Administration[37] were reported as motivators for prescribing biosimilars. Most commonly reported disadvantages were distrust in safety[10, 17, 21, 29, 31, 33], efficacy[10, 17, 21, 29, 31, 33], immunogenicity[10, 24, 29, 33] and indication extrapolation of biosimilars[10, 32-33] or the lack of clinical data on biosimilars[23, 33, 35]. Single studies also suggested the quality[10], traceability[10] or tolerability[21] of biosimilars and patients' concerns towards biosimilars[21] as disadvantages.

Initiation of biosimilars and switches between original biologic medicines and biosimilars (n=22)

Physicians (39–89%) seem more eager to prescribe a biosimilar for biologic-naïve patients rather than patients already treated with biologic medicines[10, 19-, 22, 24, 26-29, 31-37] (**Table 2**). In discrete choice experiment studies, for example, 61–84% of gastroenterologists chose biosimilar in at least one of the choice sets for biological-naïve patients[19-20]. However, there are also other factors affecting on the medicine selection, such as the cost of the medicines. It was reported, that if cost were not an issue, only 11% of physicians would choose biosimilar for treatment initiation[32]. Additionally, studies suggest that some personal characteristics may influence on the uptake of biosimilars by individual physicians. Men, senior consultants and those treating more patients[20], along with those with greater familiarity with brand name medicines and uncertainty of long-term safety of biosimilars[32] were often unlikely to choose biosimilar as initial therapy. Within medical specialties, gastroenterologists (95% with no concerns) appear most confident on using biosimilars in treatment initiations, followed by rheumatologists (92%), dermatologists (79%) and diabetologists (75%)[22].

Physicians seem less eager to switch an originator biologic medicine to a biosimilar[10, 19-24, 30-32, 35-36] (**Table 2**). The share of physicians that were willing to switch an originator to a biosimilar was 51 or below with the exception of a single study in which the percentage was 91%[10, 21, 23-24, 30, 32, 35]. Similarly to the treatment initiation, medical specialty of the individual physician may effect on the willingness to switch biologic medicines[22]. Gastroenterologists (95% with no concerns) seem most confident on switching, followed by dermatologists (78%), diabetologists (69%) and, notably, rheumatologists (53%).

Pharmacist-led substitution of biologic medicines (n=10)

Physicians (64–95%) are concerned about or disagree with pharmacist-led substitution of biologic medicines[10, 18, 21, 23-25, 29, 32-34] (**Table 2**). Studies suggest that having a full autonomy on medicine selection and being fully aware of which medicine patient receives, was often crucial for physicians[10, 25, 29, 34]. However, according to a single study, 88% of physicians believe that there will be a political change resulting to pharmacist-led substitution without consulting physicians in the future[29].

4 DISCUSSION

According to this systematic review, physicians' knowledge on biosimilars varies widely. In general, measured knowledge appears weaker than self-assessed knowledge. Physicians use multiple information sources on biologic medicines, most commonly scientific publications, pharmaceutical companies and professional societies. Similarly to their knowledge, physicians' perceptions towards biosimilars and the uptake of these medicines also vary. Physicians seem to prefer originator products to biosimilars and prescribe biosimilars mainly for biologic-naïve

patients. Physicians consider cost savings and lower price in comparison to the originator biologic medicine as main advantages of biosimilars, while doubts often relate to safety, efficacy and immunogenicity of biosimilars. Most physicians have negative perceptions towards pharmacist-led substitution of biologic medicines.

This study addresses that physicians' knowledge on biosimilars appears inadequate. This may contribute to low prescribing and uptake of biosimilars[10, 30, 33]. Although this issue has been widely recognised, there is limited evidence on the effectiveness of education interventions on prescribing[39]. On the contrary, academic detailing has proven to be effective in steering prescribing[40-41]. Academic detailing is a method in which a trained educator meets with a healthcare professional and shares the latest evidence-based information on the topic that is educated[42]. Besides its' effectiveness in steering prescribing patterns, academic detailing has been proven to improve the cost-effectiveness of prescribing and reduce medical costs[43-44]. It is vital that in the near future physicians and other healthcare professionals are provided targeted, evidence-based information on biosimilars to support the uptake and to gain the full cost-saving potential of these medicines[45-46]. The information from medical societies is also vital in the distribution of appropriate biosimilar information[11].

According to this study, physicians' attitudes towards biosimilars are contradictory and the prescribing of biosimilars is more often directed to biologic-naïve patients. This is despite of convincing evidence that supports switching[47]. Since prescribing decisions are either made by individual physicians or they are steered by policies, it is evident that more binding policies and guidance on prescribing is needed[10-11]. Countries have implemented various means to enhance the uptake of biosimilars. For example in Denmark and Norway, hospital, regional or national tendering is in use, resulting in significant savings in the purchase of biologic medicines[11, 48-49]. Some countries have implemented incentives for healthcare professionals[11]. Prescription quotas that define the ratio of biosimilars of all prescribed biologic medicines, are in use in Germany and Sweden[50], while gain-sharing agreements that enable using the savings from biosimilar uptake to be used in the benefit of the clinic or the organisation are used in Sweden and in the United Kingdom[51-52]. Pharmacist-led substitution of biologic medicines can also be seen as a potential mean to enhance the uptake of biosimilars[11, 29]. Pharmacist-led substitution is legislatively possible in France and in the United States, and for some biological medicines in Australia[53-55]. Furthermore, the implementation of pharmacist-led substitution in currently ongoing in some European countries[45, 56]. All these initiatives highlight that the issue of weak uptake of biosimilars has been acknowledged globally, and there is a need to discover sustainable means to enhance and stabilize the uptake[11]. What complicates the issue is that, for example in Europe, even though the biosimilarity between biologic medicines is stated by the European Medicines Agency, the decisions on the interchangeability and substitution are made at the national level. In order to support the uptake of biosimilars, educational measures for both healthcare professionals and patients, and national recommendations and policies for switching and substitution of biologic medicines are needed[29, 45-46].

To the authors' knowledge, systematic literature reviews on the physicians' perceptions towards the uptake of biosimilars have not been published prior to this review. However, the results of this study are concise with an earlier systematic review on healthcare professionals' perceptions on biosimilars[33]. In addition to the novel information provided by this study, main strengths of our review are that the literature search was conducted with the help of an experienced information specialist, and the quality evaluation of publications was conducted independently by two researchers in order to avoid bias[57]. Whereas one major limitation of this review was that the study-by-study data extraction was only done by one researcher. Furthermore, theses or reports by authorities that could have included research results were excluded from this study. In addition, any of the available protocols for quality assessment did not cover different types of study settings and the protocol used in this study was compiled from four separate protocols. One notable point is also that the data in the publications that were selected for this review were mainly collected in 2017 or before. The topic is very timely and perceptions towards the uptake

of biosimilars may change according to new research information and experience in using these medicines. Thus, there is a need to continue examining perceptions of physicians, particularly with qualitative research methods.

5 CONCLUSIONS

This systematic literature review concludes that physicians' knowledge on and attitudes towards biosimilars vary. Although physicians have positive attitudes towards biosimilars, prescribing is limited, especially for patients that are already treated with biologic medicines. Perceptions towards the pharmacist-led substitution of biologic medicines are often negative. Education and national recommendations and policies for switching and substitution of biologic medicines are needed to support the uptake of biosimilars.

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COMPETING INTERESTS

Authors declare no competing interests.

AUTHOR'S CONTRIBUTIONS

KS, MM, JJ and KHA contributed to the conception or study design. KS and MM acted as principal investigators in the search and evaluation of the literature and in the quality assessment. KS drafted the manuscript. All authors participated in critical revision of the manuscript and approved the final version.

PATIENT CONSENT

Not required.

ETHICAL CONSENT

Not required.

PATIENT AND PUBLIC INVOLVEMENT

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

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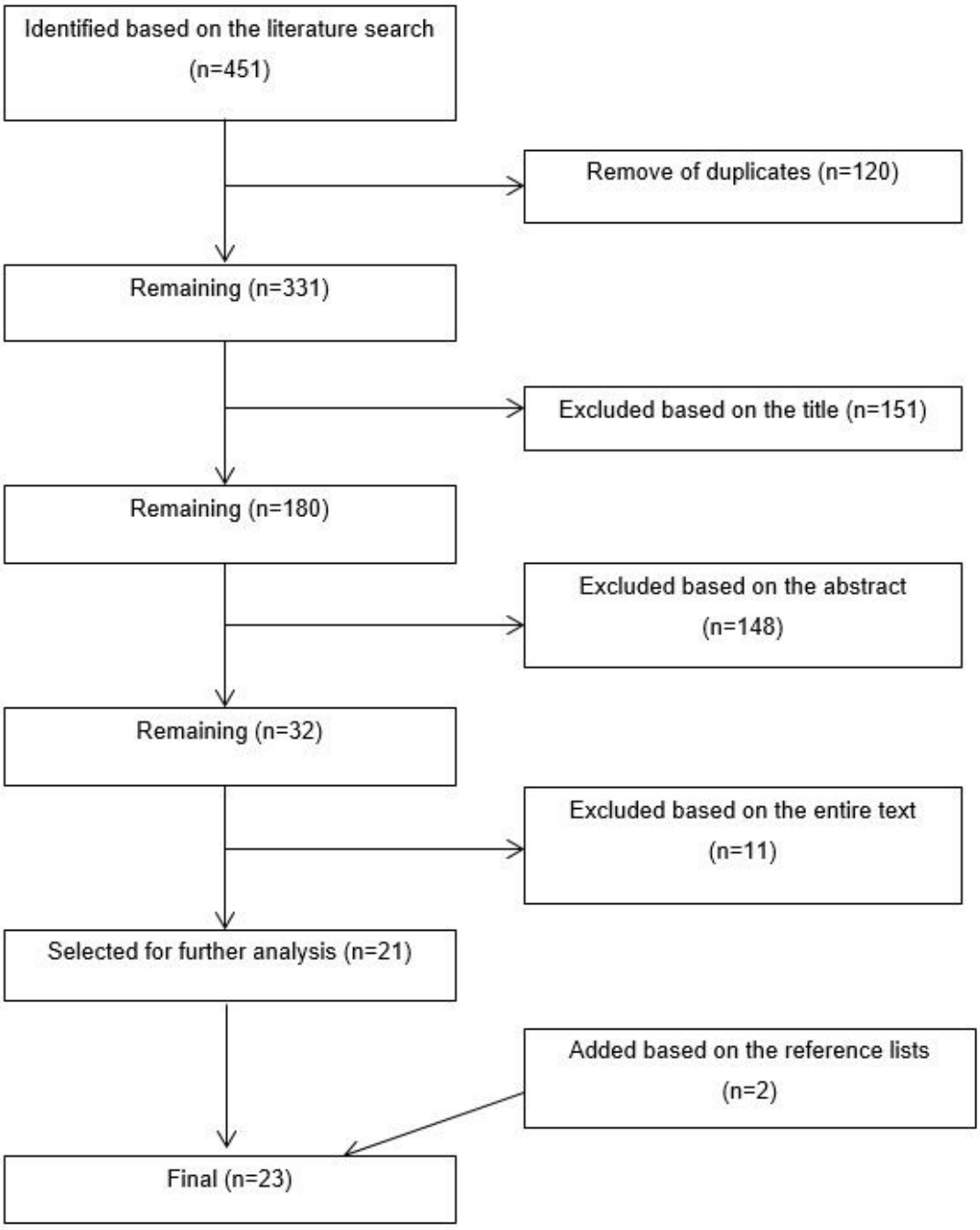

Figure 1. Flow chart on the review process.

Appendix 1. Literature search approach.

Database	Search terms
MedLine Ovid	(attitude* or stance* or opinion* or position* or orientat* or insight* or esteem* or estimat* or percepti* or belie* or decision* or decide* or determin* or prescrib* or chose* or choos* or choice* or guid* or recommend* or commission* or adopt* or accept* or uptak* best practice).mp AND (((physician.mp. or Physicians/) OR (clinician* or doctor* or specialist* or consultant*).mp.) AND (exp dermatology/ or exp internal medicine/ or exp endocrinology/ or exp gastroenterology/ or exp rheumatology/)) OR (exp general practice/ or exp family practice/ or exp general practitioners/ or exp hospitalists/ or exp physicians, family/ or exp physicians, primary care/or physician.mp. or Physicians/ or (clinician* or doctor* or specialist* or consultant*).mp.) AND (exp DIABETES MELLITUS/ or diabetes.mp.)) AND (exp Biosimilar Pharmaceuticals/ or biosimilar*.mp.) (attitude* or stance* or opinion* or position* or orientat* or insight* or esteem* or estimat* or percepti* or belie* or decision* or decide* or determin* or prescrib* or chose* or choos* or choice* or guid* or recommend* or commission* or adopt* or accept* or uptak* best practice).mp AND (((Physicians/ or (physician* or clinician* or doctor* or specialist* or consultant*).mp.) AND (exp Biosimilar Pharmaceuticals/ or biosimilar*.mp.)
Scopus	TITLE-ABS-KEY (biosimilar* AND (((physician* OR clinician* OR doctor* OR specialist* OR consultant*) W/20 (rheumatology OR gastroenterology OR endocrinology OR dermatology OR diabetes OR "internal medicine")) OR (rheumatologist* OR gastroenterologist* OR endocrinologist* OR dermatologist* OR hospitalist OR "General Practitioner*" OR physicians W/2 family)) AND (attitude* OR stance* OR opinion* OR position* OR orientat* OR insight* OR esteem* OR estimat* OR percepti* OR belie* OR decision* OR decide* OR determin* OR prescrib* OR choice* OR choos* OR chose* OR "best practice" OR guidi* OR guide* OR recommend* OR commission* OR adopt* OR accept* OR uptak*)) AND (LIMIT-TO (SRCTYPE , "j ") OR LIMIT-TO (SRCTYPE , "p ")) AND (LIMIT-TO (DOCTYPE , "ar ") OR LIMIT-TO (DOCTYPE , "re ") OR LIMIT-TO (DOCTYPE , "cp ") OR LIMIT-TO (DOCTYPE , "ip ")) AND (LIMIT-TO (LANGUAGE , "English ")) TITLE-ABS-KEY(biosimilar* AND (physician* OR clinician* OR doctor* OR specialist* OR consultant*) AND (attitude* OR stance* OR opinion* OR position* OR orientat* OR insight* OR esteem* OR estimat* OR percepti* OR belie* OR decision* OR decide* OR determin* OR prescrib* OR choice* OR choos* OR chose* OR "best practice" OR guidi* OR guide* OR recommend* OR commission* OR adopt* OR accept* OR uptak*)) AND (LIMIT-TO (SRCTYPE,"j ") OR LIMIT-TO (SRCTYPE,"p ")) AND (LIMIT-TO (DOCTYPE,"ar ") OR LIMIT-TO (DOCTYPE,"re ") OR LIMIT-TO (DOCTYPE,"cp ") OR LIMIT-TO (DOCTYPE,"ip ")) AND (LIMIT-TO (LANGUAGE,"English "))

Appendix 2. Quality assessment protocol.

Date:

Evaluator:

Authors:

Title:

Design	Yes
Meta-analysis	
Randomized controlled trial	
Systematic review	
Quantitative study: type (survey, pilot, other)	
Qualitative study: type (interview, focus group, other)	
Other, what?	

	Yes (1p)	Partly (½p)	No (0p)	Notes
Aim and context				
1 Is there an explicit aim?				
2 Is the context described?				
Methodology				
3 Is the data collection described accurately and is it repeatable?				
4 Is the sample selection preventative/relevant/not strategic (sample selected intentionally)?				
5 Is the dropout described?				
6 Is the data analysis described accurately and is it repeatable?				
7 Are the (statistical or other) methods adequate and applicable in relation to the aims of the study?				
Results				
8 Are the findings logic, reliable and clearly displayed?				
Discussion and conclusions				
9 Is there a critical discussion on the findings?				
10 Is there a critical discussion on the method?				
11 Is there a new value?				
12 Are the aims of the study met in the results and findings of the study?				
13 Are the instruments valid?				
14 Are the instruments reliable?				
Ethics				
15 Is there an ethical discussion?				
16 Are the authors non-dependable and free of any conflicts of interest?				
17 Did the participants participate without receiving a fee?				
TOTAL POINTS				

Quality assessment (rounded upwards when necessary): high: ≥ 15 yes, moderate: 12-14.5 yes, low: < 12 yes

Quality assessment protocol adapted from the protocols of Åkesson et al. (2006), Tong et al. (2007), Joanna Briggs Institute (2014) and Swedish Agency for Health Technology Assessment and Assessment of Social Services (2016).

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Section
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Abstract, material and methods
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☒	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Affiliations section
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Material and methods, Appendix 2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Funding section
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Funding section
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Funding section
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Introduction

Section/topic	#	Checklist item	Information reported		Section
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Last chapter of the Introduction and Data extraction and analysis chapter
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Table 1
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Literature search section
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Material and methods
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Material and methods
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Material and methods
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐	☒	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Material and methods, especially Quality assessment
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	Material and methods, especially Quality assessment
DATA					

Section/topic	#	Checklist item	Information reported		Section
			Yes	No	
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Tabulation, see Table 2
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	Tabulation, see Table 2, and Material and methods
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Table 3
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Table 3, Material and methods

BMJ Open

Physicians' perceptions on the uptake of biosimilars - A systematic review

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Primary Subject Heading:	Health policy
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Keywords:	biosimilar, biologic medicine, physician, perception

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Physicians' perceptions on the uptake of biosimilars - A systematic review

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ABSTRACT

Objectives: Examine physicians' perceptions on the uptake of biosimilars

Design: Systematic review

Setting: Literature search in MedLine Ovid and Scopus databases at the end of 2018. Search resulted to 451 studies and after removal of duplicates, to 331 studies. Two researchers examined studies based on the title, abstract and the entire text. Twenty-one scientific original studies written in English that addressed physicians' perceptions on the uptake of biosimilars were selected for further analysis. Additionally, the references of included studies were screened and two studies were handpicked and included in this review. Data of these 23 studies were extracted study-by-study basis. All publications were quality assessed by two researchers. In this review, higher emphasis was given to publications with high-assessed quality.

Results: Majority of selected studies were conducted in Europe and they commonly utilized short surveys. Physicians' familiarity of biosimilars varied: 49–76% were familiar with biosimilars and 2–25% did not know what biosimilars were, percentages varying from study to study. Measured knowledge appeared weaker compared to self-assessed knowledge. Physicians' perceptions towards biosimilars also varied: 54–94% were confident prescribing biosimilars, while 65–67% had concerns regarding these medicines. Physicians seem to prefer originator products to biosimilars and prescribe biosimilars mainly for biologic-naïve patients. Physicians consider cost savings and lower price in comparison to the originator biologic medicine as main advantages of biosimilars, while doubts often relate to safety, efficacy and immunogenicity. 64–95% of physicians have negative perceptions towards pharmacist-led substitution of biologic medicines.

Conclusions: Physicians' knowledge on and attitudes towards biosimilars vary. Although physicians had positive attitudes towards biosimilars, prescribing is limited, especially for patients that are already treated with biologic medicines. Perceptions towards the pharmacist-led substitution of biologic medicines are often negative. Education and national recommendations for switching and substitution of biologic medicines are needed to support the uptake of biosimilars.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first systematic review conducted solely on physicians' perceptions regarding the uptake of biosimilars
- The literature search was conducted with the help of an experienced information specialist
- Publications selected for this review were quality evaluated by two researchers independently
- The quality evaluation protocol was compiled from four existing evaluation protocols
- The data in the studies included in this review was mainly collected before

KEYWORDS
biosimilar, biologic medicine, physician, perception, systematic review

1 INTRODUCTION

Biologic medicines consist of one or multiple biologic active substances and are often manufactured through biotechnology[1-2]. Biologic medicines were first developed mainly for rare diseases, but have thereafter improved the treatment of many common diseases, such as diabetes, arthritis and psoriasis[1]. The flipside of this transformation are high costs of biologic medicines that have contributed to increased medical costs globally[3].

Biosimilars are biologic medicines highly similar to the originator biologic medicines with same standards on the quality, safety and efficacy of the products[2-4]. Biosimilars have no clinically meaningful differences to the existing reference product. Biosimilars are not regarded as generic medicines due to the complex manufacturing process and the natural variability between manufacturing batches of biologic medicines. The comparability of the product to the reference product has to be demonstrated, however, clinical trials are not required. As a result, biosimilars can be brought to the market at a lower cost in comparison to the originator biologic product. The uptake of biosimilars could lead to healthcare cost savings and better patient access to costly biologic therapies[5]. Until the end of 2018, 50 biosimilars have received marketing authorisation in Europe and 15 in the United States[6-7].

Regardless of their demonstrated comparability and their cost-saving potential, biosimilars have not fully penetrated the market of biologic medicines. The European Union holds 80% of the global biosimilar market, but biosimilars constitute only 1% of total sales of biologic medicines[8-9]. It has been stated that the decisions to select biologic medicines may be either policy driven or made by individual physicians, which has raised a need to assess the prescribing of biosimilars in a critical manner[10-11]. Physicians' reluctance to prescribe biosimilars may restrain potential savings in medical costs that could enable offering biologic treatment to larger patient populations and providing more cost-effective treatment, as similar benefits could be gained by using less expensive treatments. Therefore, it is vital to study physicians' attitudes towards and perceptions on the uptake of biosimilars. This topic has not been reviewed systematically, and published information on the topic is somewhat contradictory. The aim of this systematic review was to examine physicians' perceptions on the uptake of biosimilars.

2 MATERIAL AND METHODS

Literature search

A systematic literature search was conducted in MedLine Ovid and Scopus databases at the end of 2018. Selected databases provide a comprehensive selection of scientific publications from the disciplines of pharmacy and medicine. The systematic search strategy (**Appendix 1**) was constructed by the research group and the search was conducted by an experienced information specialist.

The initial search resulted in 451 studies. After removal of duplicates (n = 120), 331 studies remained. Studies were examined based on the title, abstract and the entire text by two researchers independently (KS and MM). Of the 331 studies, 151 were excluded based on the title, 148 based on the abstract and 11 based on the entire text. At each stage, researchers shared their views of the studies, discussed on possible differences on opinions and reached a consensus opinion based on the discussion. The inclusion and exclusion criteria of this systematic review are presented in **Table 1**. A total of 21 publications were selected for further analysis. Furthermore, the reference lists of these 21 articles were screened and two further articles that met the inclusion criteria were

handpicked and included in this review, which brings the final number of included studies being 23. The PRISMA flow chart explaining the study inclusion process is presented in **Figure 1**.

Table 1. Inclusion and exclusion criteria of studies of this systematic review.

Inclusion criteria	Exclusion criteria
• Original primary studies	• Other than original primary studies, such as reviews, conference papers, consensus papers, commentaries and letters to editors
• English language	• Other language than English
• Investigating physicians' perceptions on the uptake of biosimilars (physicians in particular or at least 45% of physicians among other healthcare professionals, although only physicians perceptions were taken into account in this review)	• Investigating other healthcare professionals' perceptions on the uptake of biosimilars or publications with less than 45% of physicians of all participants involved or in which the physicians' perceptions are not separated in the results of the study
• Publications on the physicians' perceptions on the automatic substitution of biologic medicines	• Publications on the physicians' perceptions on the automatic or generic substitution of other medicines than biologics

Quality assessment

Each of the 23 selected studies was concisely reviewed. Quality assessment was conducted according to a protocol adapted from the protocols of Åkesson et al. (2006), Tong et al. (2007), Joanna Briggs Institute (2014) and Swedish Agency for Health Technology Assessment and Assessment of Social Services (2016)[12-15] (**Appendix 2**). Adapted protocol was developed and used in the quality evaluation, because the study designs of the included studies varied and there was no single protocol that was suitable for evaluating the studies in a consice manner. Two researchers (KS and MM) conducted quality assessments individually and then compared their reviews. Differences in opinions (n = 6) were discussed and final evaluation was set in consensus. In the Results section of this systematic review, studies that were assessed as having high quality are emphasized in comparison to the results of those with moderate or low assessed quality.

Data extraction and analysis

A meta-analysis was not conducted due to the various methods and both qualitative and quantitative approaches applied in the studies that were included in this review. The following information was extracted from all included studies: general information (authors, year of publication, and country of publication), aims, methods and results. In regards to results, seven topics for data extraction were identified based on the topics discussed in the publications and on the discussion in the research group. These topics were: physicians' 1) self-rated knowledge of biosimilars, 2) measured knowledge on biosimilars, 3) information sources of biologic medicines, 4) attitudes towards and experienced advantages and disadvantages of biosimilars, 5) actions in the initiation of biosimilars for biologic-naïve patients, 6) actions in the switches between originators and biosimilars for patients already treated with biologic medicines and 7) thoughts on pharmacist-led substitution of biologic medicines. In the Results section of this systematic review, these seven topics are presented within four broader themes: physicians' 1) self-rated and measured knowledge on biosimilars and information sources on biologic medicines, 2) attitudes towards and experienced advantages and disadvantages of biosimilars, 3) perceptions on the treatment initiations with biosimilars and on the switches between originator biologic medicines and biosimilars and 4) attitudes towards pharmacist-led substitution of biologic medicines. All percentages presented in the article refer to the percentages shown in the included studies of physicians with a certain opinion If more than one study investigated the topic, a range of persentages in these studies are shown.

3 RESULTS

Study characteristics

Physicians' perceptions on biosimilars have been studied mainly in Europe (n = 15)[10, 16-28] and North America (n = 4)[29-32]. Single studies have been conducted in both Europe and North America (n = 1)[33], Australia (n = 1)[34], New Zealand (n = 1)[35], Central and South America (n =1)[36] and in multiple African, European and Middle Eastern countries (n = 1)[37] (**Table 2**). All studies were published between 2014 and 2019, but majority of them (n = 19)[10, 16, 19-21, 23-32, 34-37] in 2017 or before. With the exception of a single publication[33], the data presented in the studies were collected between 2013 and 2017. Most of the 23 selected publications utilized surveys, typically web-based questionnaires with 11–22 questions, or fully structured short interviews (n = 16)[10, 16-17, 21-24, 25-26, 29-30, 32, 34-37]. In addition there was a qualitative interview study[18] and real-world cross-sectional studies (n = 2)[27-28], in which physicians filled a survey form and reported their prescribing and after, recruited patients that also filled a questionnaire form to provide information on how reported prescribing actualized in practice. There were also discrete choice method surveys (n = 2)[19-20], in which prescribers were given a hypothetical scenario and possible treatment options, and they were asked to choose the alternative they prefer[38]. Furthermore, one systematic literature review on healthcare professionals' perceptions on biosimilars[33], and one literature review with survey on the market uptake of biosimilars[31], have been conducted.

Quality assessment

Of 23 included studies, nine[10, 17, 19-20, 22, 26, 32-33, 35] were evaluated to be high, five[18, 21, 27-29] to be moderate and nine[16, 23-25, 30-31, 34, 36-37] to be low in quality based on criteria used in this review (**Table 3**). Publications evaluated to be high in quality often included well-described and logically presented methods and results sections and a critical discussion section, of which those evaluated to be moderate or low quality typically lacked. In general, the quality assessment revealed that there is a lack of valid instruments and studies utilizing qualitative research methods.

Self-rated and measured knowledge on biosimilars and sources of information (n = 18)

There is variation on the physicians' self-rated knowledge on biosimilars (**Table 2**). In individual studies, physicians consider they have at least a basic understanding of the topic: 5–44% of the physicians reported that they feel very familiar and 49–76% that they feel familiar with biosimilars[10, 23, 25-26, 29, 32, 34-36]. In these studies 2–25% of the physicians reported that they do not know what biosimilars are. In individual studies, physicians with more years of practice and those with specialisation consider themselves more familiar with biosimilars in comparison to less experienced colleagues and general practitioners[10, 21, 32]. On the contrary, a prior systematic literature review states that physicians often think that they only have little knowledge on the topic and that years of practice do not significantly affect prescribing behaviour[33].

Although physicians self-rate that they generally feel familiar with biosimilars, the measured knowledge on the topic appears weaker (**Table 2**). 18–66% of the physicians incorrectly described biosimilars as generic medicines and 31–72% as structurally identical to originator medicines[10, 21-22, 24, 30, 32, 34, 36-37]. However, in three studies, 76–100% of physicians were able to share the complete definition of a biosimilar correctly[17-18, 26].

Table 2. Characteristics of the 23 studies included in this systematic review.

Reference (Country or region)	Aims and methods	Results						
		Self-rated knowledge	Measured knowledge	Information sources	Attitudes towards and experienced advantages and disadvantages of biosimilars	Initiation of biosimilars (biologic-naïve patients)	Switches between originators and biosimilars (patients already treated with biologicals)	Pharmacist-led substitution of biologic medicines
Akhmetov et al. 2015[16] (Ukraine)	Endocrinologists', oncologists', nephrologists', immunologists' and rheumatologists' awareness of biosimilars Short interviews with eight close-ended questions, including 6 Likert-type items (n = 82), time of the study not reported	Low to medium levels (not reported more specifically) of biosimilar awareness on a 1-5 scale, where 1=low and 5=high) Endocrinologists and nephrologists had higher levels of awareness than other respondents	N/A	Peer-reviewed journal articles (n = 35), internet (n = 31), medical conferences (n = 20), popular press (n = 9), key-opinion leaders (n = 3), drug manufacturers (n = 2)	On a 1-5 scale, likelihood of prescribing biosimilars: 68% average (specific numbers not reported), 23% below average and 9% above average Majority (n not reported) are likely to try biosimilars in small batches, and then gradually move to larger groups of patients, endocrinologists and nephrologists showing the greatest interest Facilitators of prescribing: 39% cost advantage, 22% certification of safety by EMA or FDA, 22% certification of efficacy by EMA or FDA, 10% propitiousness of the Cabinet of Ministers and 7% trust towards European, American and Japanese biotech companies as importers Majority (n not reported) required 40-50% lower price for biosimilars than original biologics, endocrinologists typically accepting 20-30% discount in comparison to rheumatologists and oncologists that anticipated over 50% discount	N/A	N/A	N/A
Aladul et al. 2019[17] (the United Kingdom)	Knowledge and attitudes of healthcare professionals (n = 150 dermatologists, diabetologists, gastroenterologists and rheumatologists) towards infliximab and insulin glargine biosimilars Web-based survey via selected medical associations between August 2016 and January 2017	80% were aware that biosimilars were available on their local formulary	76% correctly considered biosimilars as copies of originators	N/A	91% considered robust pharmacovigilance studies and 84% the costs as the most important influencer of their prescribing of biosimilars	22% had major concerns on the efficacy and 14% on the safety of biosimilars that prevented them of starting a biosimilar	50% had major concerns on the efficacy and 34% on the safety of biosimilars in the switches	N/A
Aladul et al. 2018[18] (the United Kingdom)	Perceptions of consultants with specialties of diabetes mellitus, ulcerative colitis, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis (n = 10) towards biosimilar infliximab, etanercept and insulin glargine and potential barriers and facilitators to their prescribing Semi-structured interviews of purposive convenience sample of West Midlands hospital staff between June-November 2017	N/A	All interviewees expressed an understanding of the concept of biosimilars and believed biosimilars were copies of originators	Conferences, pharmaceutical industry representatives, scientific journals and colleagues	Majority of rheumatologists and diabetologists (n not reported) would prescribe the reference product if the prices of the reference product and the biosimilar are equal Gastroenterologists expressed more confidence and fewer concerns than other specialists, stating that indication extrapolation had previously been the major obstacle in the biosimilar uptake, but that it had been overcome Majority of rheumatologists (n not reported) had concerns on indication extrapolation, considering their patients are very sensitive with higher multimorbid risks. Some rheumatologists (n not reported) openly declared being mistrustful on biosimilars Facilitators of prescribing were information from societies, authorities and national registries. Barriers of prescribing were unexpected adverse effects or increase in side effects, patients' reluctance on using biosimilars, complicated, unsuitable or non-user-friendly administration device, unavailability of dose strengths in comparison to originators	Majority (n not reported) were content to initiate biosimilars Minority of rheumatologists and diabetologists (n not reported) felt under pressure to initiate new patients with biosimilars by their organization Two rheumatologists were happier to initiate biosimilars rather than switching	All gastroenterologists (n = 7) and a minority of rheumatologists (n not reported) were content to switch patients from reference products to a biosimilar All those that were content with switching considered that patients should be given the choice between the products Majority of all physicians (n not reported) felt multiple switching based on cost reasons irrational	Majority (n not reported) has negative view on the pharmacist-led substitution of biologic medicines Minority (n not reported) considered that automatic substitution would be accepted in the next few years
Baji et al. 2016a[19] (Hungary)	Gastroenterologists' treatment preferences in ulcerative colitis Discrete choice experiment survey (in which prescribers are given hypothetical scenario and possible treatment options, and they are asked to choose the alternative they prefer[39]) in a Hungarian professional society meeting in 2014 (n = 51)	N/A	N/A	N/A	20% had no concerns on biosimilars, 67% had some concerns on efficacy and/or safety and 12% did not support the use of biosimilars due to the lack of RCT evidence	84% of all physicians and 80% of those who had some concerns (67%) chose biosimilar in at least one choice set The most important attribute driving the choice: stopping rule (whether treatment after 12 months is reimbursed) Estimated probability of choosing the originator over biosimilar in the present reimbursement situation: 48%. Probability of choosing the biosimilars with all the benefits offered over the originator in the present situation: 85% versus 15%	61% of all and 53% of those who were concerned chose biosimilar in at least one of the choice sets The most important attribute driving the choice: stopping rule Estimated probability of choosing the originator over biosimilar in the present reimbursement situation: 71%. Probability of choosing the biosimilars with all the benefits offered over the originator in the present situation: 63% versus 37%	N/A

Baji et al. 2016b[20] (Hungary)	Gastroenterologists' treatment preferences in Crohn's disease Discrete choice experiment survey (in which prescribers are given hypothetical scenario and possible treatment options, and they are asked to choose the alternative they prefer[39]) in a Hungarian professional society meeting in 2014 (n = 51)	N/A	N/A	N/A	20% had no concerns on biosimilars, 65% had some concerns on efficacy and/or safety and 12% did not support the use of biosimilars due to the lack of RCT evidence Four clinicians were classified to "No biosimilar" attitude group, 19 to the "Biosimilar to new patients only" group and 27 to the "Biosimilar" group (one clinician was excluded from the analysis)	Men, senior consultants, working in inflammatory bowel disease centre and treating more patients were more likely to consider biosimilars for biologic-naïve patients only Estimated probability of choosing the originator over biosimilar, when no benefits are offered for using the biosimilar: 60%. Probability of choosing the biosimilar with all kinds of benefits over the originator: 89% versus 11% The most important attribute driving the choice: continuity of medicine supply	Estimated probability of choosing the originator over biosimilar, when no benefits are offered for using the biosimilar: 74%. Probability of choosing the biosimilar with all kinds of benefits over the originator: 44% versus 56% The most important determinant of choice: type of the treatment	N/A
Barsell et al. 2017[29] (USA)	Dermatologists' knowledge and perceptions of biosimilars, whether a practice gap exists and to study misconception and barriers to biosimilar usage Web survey of 14 multiple-choice questions for the members of five state dermatologic societies and National Psoriasis Foundation in 2015 (n = 97)	62% responded having basic understanding of biosimilars, 27% complete understanding and 11% that they have never heard of biosimilars	37% were aware that biosimilars are highly similar to the reference product, 26% described biosimilar as "generic", 27% described them as same bio-drug with equal bioequivalence and 10% said they did not know the definition. Those with complete understanding (27%), 21% incorrectly described biosimilar as "generic"	35% self-study, 25% scientific publications, 17% conferences and seminars, 3% biosimilar company-sponsored events and 20% other	Advantages: 71% low price to patients, 68% easier access to treatment and 65% low price to payers. Disadvantages: 71% efficacy, 66% potential switch to biosimilar without physicians' knowledge, 66% safety and 63% immunogenicity. 8% believed there were no advantages Convincing physicians of interchangeability: 44% extensive phase I, II and III studies, 37% valid longitudinal data from patient registries, 37% same level of testing (not specified more thoroughly) than generic medicines, 36% evidence of pharmacokinetic and pharmacodynamic equivalence	25% definitely or highly likely to prescribe a biosimilar 38% will try it on very selected patients	N/A	88% believed that there will be a political change resulting to pharmacist-led substitution without consulting physicians in the future 76% very important and 18% somewhat important to have control over whether patients receive originator or biosimilar
Beck et al. 2016[21] (France)	Knowledge, experience and opinions related to biosimilars and to identify expectations, barriers and possible options to promote prescription Web survey of 22 questions for nearly 500 rheumatologists in 2015 (n = 116)	55%/3% considered they had little/no knowledge of biosimilars 5% felt very well-informed Hospital-based rheumatologists were likely to be more familiar with biosimilars compared to office-based rheumatologists 98% had at least one question about biosimilars	85% thought biosimilars are similar to reference products that had gone off-patent; 85% considered biosimilars have no meaningful differences in quality, 80% in safety and 90% in efficacy; 65% thought that the assessment of biosimilarity requires more comprehensive data than generic drugs; and 46% believed that biosimilar marketing authorisation is granted on the sole investigation of pharmacokinetic bioequivalence	84% self-study and scientific publications, 76% pharmaceutical companies, 72% continuous training, 54% physician colleagues and 19% pharmacist colleagues	44% agree and 10% strongly agree being in favour of implementation of biosimilars Positive factors: 90% healthcare cost savings, 61% releasing of resources allowing treating additional patients, 49% positive impact on patients' access to innovative medicines and 46% health policy-makers incentives. Barriers: 67% indication extrapolation of efficacy and safety, 66% lack of information about tolerability, 59% risk of increasing patients' concerns, 57% lack of clinical trials and 55% patients' wishes to be treated with the originator	7% had already prescribed biosimilars mentioned in the survey 89% considered it was conceivable to start a treatment for biologic-naïve patients	25% could envision a switch	58% strongly disagree and 23% disagree of approving substitution by a pharmacist
Chapman et al. 2018[22] (the United Kingdom)	Healthcare professionals' knowledge and attitudes towards infliximab and insulin glargine biosimilars and factors influencing their prescribing and compare healthcare professionals' attitudes with the utilisation of these biosimilars in hospitals Web-based survey of 11 questions for societies of dermatology, diabetology, gastroenterology and rheumatology in 2016-2017 and drug utilisation analysis from DEFINE database in 2015-2016 (n = 234). Other stakeholders apart from physicians are not addressed in this review	N/A	72% correctly thought biosimilars are similar copies of biologic medicines, 18% thought biosimilars are generic biologic medicines, 3% counterfeit medicines, 3% had heard of them but did not know what they were, 3% had never heard of them and 1% new biological medicines 75% knew biosimilars were available on their local formulary	N/A	Gastroenterologists were most frequent prescribers of biosimilars (prescribing every day or week), followed by rheumatologists, diabetologists and dermatologists The dominant consideration: cost saving Increasing the use of biosimilars: regulatory guidance and robust pharmacovigilance studies, local policy, potential cost saving to organisation (whether or not savings were invested in the prescribers' department) and robust cost-effectiveness data of biosimilar vs. originator	95% and 90% of gastroenterologists, 92% of rheumatologists, 79% of dermatologists and 75% of diabetologists had no or minor concerns on safety 90% of gastroenterologists, 88% of rheumatologists, 74% of dermatologists and 68% of diabetologists had no or minor concerns on efficacy	95% of gastroenterologists, 53% of rheumatologists, 78% of dermatologists and 69% of diabetologists had no or minor concerns on safety 93% of gastroenterologists, 55% of rheumatologists, 79% of dermatologists and 65% of diabetologists had no or minor concerns on efficacy	N/A
Cohen et al. 2016[30] (USA)	Dermatologists', gastroenterologists', haematologist-oncologists', medical oncologists', nephrologists' and rheumatologists' awareness, knowledge, and	N/A	92% of dermatologists, 90% of gastroenterologists, 83% of rheumatologists, 74%	88% scientific journals, 73% FDA and 64% physician peers. Trust to media was less than 5%	Generally positive attitudes towards biosimilars. Dermatologists and rheumatologists appear less enthusiastic	N/A	91% open to switching patients to a biosimilar	N/A

	perceptions of biosimilars over time (survey will be repeated in 2-3 years) Survey of 19 questions in 2015-2016 (n = 1201)		of nephrologists, 69% of haematologist-oncologists and 63% of medical oncologists were aware which of the listed medicines in their specialty were biologic 56% of rheumatologists, 33% of gastroenterologists, 31% of dermatologists, 15% of nephrologists, 9% of medical-oncologists and 3% of haematologist-oncologists incorrectly reported there are no biosimilars available		62% considered the biosimilar will have equivalent efficacy as its originator and 57% that the biosimilar will be at least as safe as the originator 58% had concerns on patient compliance and access to treatments options with originators Positive factors: increased access and utilization of biologic medicines, expanded treatment options and provided savings for the healthcare system			
Danese et al. 2016[23] (Europe, countries not reported)	Evolution on thinking about biosimilars one year after they had become available in the EU. Comparison to the survey published by Danese et al. 2014[24] Web survey with 14 multiple-choice questions for members of European Crohn's and Colitis Organization in 2015 (n = 118)	56% judged that educational activities that they were exposed to was fair and adequate, while 16% found it unnecessary	N/A	More information was hoped from 75% medical societies, 52% multispecialty safety registries, 47% health institutions and 26% guidelines	29% totally confident, 18% very confident and 34% confident enough (5%, 8% and 26% in 2013) to prescribe a biosimilar Main advantage: 92% (90% in 2013) cost-sparing. Main issue: 42% the lack of data from clinical trials for all indications 27% (67% in 2013) consider biosimilars have higher immunogenicity compared to the originator and 17% (43% in 2013) different action than the originator 51% (24% in 2013) thought biosimilar should be approved for all the indications of the originator	N/A	44% (6% in 2013) would switch a patient with remission	89% (85% in 2013) disagreed with automatic substitution by a pharmacist 13% support substitution for new prescriptions and 13% for all patients
Danese et al. 2014[24] (Europe, countries not reported)	Awareness of and readiness to use biosimilars Web survey of 15 questions for 1,000 randomly selected European Crohn's and Colitis Organization members in 2013 (n = 307)	N/A	70% were aware that biosimilar is a similar copy, but not equal to the originator, 19% responded that it is a copy of biological agent, identical to the originator, like a generic	Preferred information: 81% multi-specialty international safety registries to monitor safety and effectiveness, 78% health institutions on the development of rules on the use of biosimilars, 66% medical societies, 61% data regarding the registration process for biosimilars and 57% multispecialty practice guidelines	6% thought that the originator and biosimilar were interchangeable The main advantage: cost-sparing (89%). The main issue: different immunogenicity pattern than the originator (67%) 50% agreed biosimilars can significantly reduce healthcare costs, 27% expected them only having a marginal impact, 6% expected additional costs of introduction, regulation and pharmacovigilance to offset any potential savings 24% agreed that the tested biosimilar could be approved for all indications of the originator in terms of safety and efficacy, 19% for all rheumatologic indications, 14% for the specific indication only, 3% stated that all biosimilars could be approved for all indications of the originator and 39% disagreed with all of the above	61% felt little or no confident in using biosimilars in their everyday clinical practice, 26% confident enough, 8% very confident, and 5% totally confident	28% would consider replacing originator with a biosimilar	64% against the substitution by pharmacist 18% would agree only for new patients
Farhat et al. 2016[37] (Algeria, Belgium, Egypt, Iran, Iraq, Italy, Jordan, Lebanon, Sudan and Syria)	Parameters on the acceptance and future prescription of biosimilars and worldwide situation focusing mainly on the EU and US laws, regulations and legislative pathways, pricing and challenging market access Survey for over 150 healthcare professional in the conference meeting in 2015 (n = 117 health care professionals responded, of which most were physicians; exact number of physicians who responded not reported). Other stakeholders apart from physicians are not addressed in this review	N/A	66% knew what biosimilars were, 12% did not know and 22% had not answered the question. Of those who knew (66%), 62% considered biosimilars bioequivalent to originator and have all preclinical and clinical trials equal to the originator 63% agreed that biosimilars are already marketed in the Arab and Middle Eastern markets, while 45% agreed that they are manufactured in the same region	N/A	Drivers for prescribing: 69% FDA or EMA approval, 65% lower price of bioequivalence in comparison to the originator, 48% bio-efficacy, 42% safety and 31% good manufacturing practices and high reputation of the manufacturer. 5% think biosimilars don't have advantages 35% considered the cost of treatment should not overcome its effectiveness or safety/tolerance 26% thought lower prices were good news as patients will be treated with biologics 27% consider biosimilars would bring cost savings 49% trust companies highly experienced in manufacturing small-molecule generic drugs and 55% companies with prior experience in manufacturing biologics as biosimilar producers	41% prescribe biosimilars while 33% don't (note that respondents were also other than physicians)	N/A	N/A
Felix et al. 2014[31] (USA)	Challenges and opportunities of market uptake of biosimilars from the perspectives of physicians and payers Survey for physicians that had written about or were familiar with biosimilars based on literature	N/A	N/A	N/A	Almost all physicians (n not reported) believed that if biosimilar was approved by FDA it will perform similarly to the originator with regard to safety and efficacy Influences of decision making: efficacy and safety, out-of-pocket costs to the patient, price of treatment and immunogenicity	Four physicians are somewhat likely, six very likely and three not likely to prescribe a biosimilar to a new patient	31%/61% (n not reported) say they are somewhat likely/very likely to switch an existing patient from originator to biosimilar	N/A

	review of Medline-indexed publications (n = 14). Other stakeholders apart from physicians are not addressed in this review				50% (n not reported) consider it is very important that there are proven chemical and pharmacokinetic similarities between originators and biosimilars Roughly half (n not reported) consider payer and cost considerations very important			
Gewanter & Reilly 2014[36] (Argentina, Brazil, Colombia and Mexico)	Understanding of biosimilars, how they use them and their concerns for the future Web-based survey for 6650 prescribers from global market research panel (n = 399)	35% did not consider themselves familiar with biosimilars, meaning they could not define them or had never heard of them	49% were aware of differences between biologicals, biosimilars and non-comparable biologicals. 30% were unaware that clinical trials for single indication lead to approval for multiple indications	71% seminars and conferences, 55% self-study, 32% education from biosimilar companies, 18% clinical trial participation and 4% other means 37% would like to learn from pharmaceutical companies	88% prescribe biologicals	50% said they believed if two biological medicines had the same non-proprietary scientific name, patient could receive either product and have the same result	44% said they believed if two biological medicines had the same non-proprietary scientific name, patient could be safely switched during a course of treatment, and the patient would have the same result 64% would not be comfortable switching for cost reasons rather medical reasons	N/A
Grabowski et al. 2015[32] (Canada)	Gaps in knowledge and attitudes towards biosimilars of rheumatologists Web-based survey of 29 questions for 369 members of Canadian Rheumatology Association in February 2014 (n = 81)	31% indicated themselves being familiar or very familiar with biosimilars Those with greater than 20 years of practice were significantly more likely to indicate themselves familiar or very familiar than those with 20 or less years of practice	66% considered biosimilars essentially same as generic drugs 38% were aware of Health Canada's guidance on clinical requirement for biosimilar approval	N/A	94% generally comfortable prescribing biologic medicines to their patients 31% comfortable prescribing biosimilars to their patients if biosimilar was currently available 29% declined until their colleagues recommend it 42% indicated a 30% price reduction, and a third a ≥50% price reduction being reasonable before payers mandated the use of biosimilars over brand name biologics 54% disagreed or strongly disagreed, 32% agreed or strongly agreed and 14% were neutral using biosimilars with extrapolated indications 49% not confident, 19% confident or very confident, and a third neutral on the long-term sustainability profile of the biosimilar with 30 weeks of head-to-head clinical trial	59% consider offering biosimilars, if biosimilar demonstrates that it is comparable to the brand name drug 72% unlikely or very unlikely, 11% likely or very likely and 16% neutral to offer a biosimilar, when biologic-naïve patient is an ideal candidate, where cost is not an issue Greater familiarity with established brand name drugs and uncertainty over the long-term safety of biosimilars were often cited among those unlikely or very unlikely offering biosimilars 54% did not typically prescribe a biosimilar, were likely or very likely to offer a biosimilar, when the provincial payer or insurance company mandated using a biosimilar	7.5% consider switching, if biosimilar demonstrates that it is comparable to the brand name drug	88% concerned or very concerned if a pharmacist had the ability to substitute a biologic drug for a biosimilar without the physician's approval
Hemmington et al. 2017[35] (New Zealand)	Perceptions and attitudes towards efficacy, safety and manufacturing of biosimilars, factors associated with positive attitudes, indication extrapolation and switching, and circumstances in which physicians would be reluctant to prescribe biosimilars E-mail survey for 327 physicians in medical specialist society (n = 110)	76% reported being familiar and having basic understanding and 13% very familiar and complete understanding of biosimilars, 9% had heard of biosimilars, but could not define them, and 2% had never heard of biosimilars	N/A	N/A	70% very or somewhat confident of the efficacy of biosimilars Less than 20% had negative views Situations when biosimilars were not prescribed: 32% lack of clinical data, 17% evidence of adverse effects or lack of efficacy, 15% patients do well with current treatment and 6% patients have complex medical history 47% very confident or somewhat confident, 32% not confident and the remainder undecided in indication extrapolation	71% would prescribe biosimilars for all or some clinical conditions meeting the relevant criteria, 10% would do this for only few or no clinical situations	51% confident and 28% not very confident or not at all confident to switch patients	N/A
Leonard et al. 2019[33] (Europe and USA)	Healthcare provider knowledge, perceptions, and prescribing behaviours of biosimilars and, need for clinician-directed biosimilar education Systematic literature review in PubMed, Embase, and Cochrane Library databases from January 2014 to March 2018 (n = 20 publications). Other stakeholders apart from physicians are not addressed in this review	Physicians often described having only little knowledge on biosimilars The shares of described having a good knowledge were low. Those that described having a high level of familiarity with biosimilars, often incorrectly defined biosimilarity, reflecting the discrepancy between claimed and actual knowledge	Majority of physicians (in different studies that were included in the systematic review) had incomplete or basic understanding of biosimilars Familiarity of biosimilars appeared greater in hospital-based clinicians than office-based clinicians	Self-study, peer-reviewed journals, professional guidelines, discussion with physician and pharmacist colleagues, manufacturer promotional material, educational programs and conference/ seminar attendance	Physicians were hesitant about the safety, efficacy and indication extrapolation of biosimilars. Safety concerns often related to immunogenicity and indication extrapolation concerns to the lack of clinical trials. Years of practice did not significantly effect on prescribing behaviour	Biosimilars were largely considered second-line therapies for biologic-naïve patients Some physicians would limit the use of biosimilars to a small patient population first	N/A	Physicians were mainly hesitant about pharmacy-driven substitution of biologic medicines Some studies reported that physicians were unaware that interchangeability could enable pharmacist-led substitution There were only some studies reporting positive attitudes towards pharmacy-led substitution
O'Callaghan et al. 2017[10] (Ireland)	Medical specialists', general practitioners' and community pharmacists awareness of and attitudes to biosimilars	44% of medical specialists and 5% of general practitioners very familiar with biosimilars, 41% and	25% of medical specialists and 18% of general practitioners considered biosimilars	Medical specialists (n = 101, not all answered this question): 72% guidelines from professional societies, 68% published	59% of those aware of biosimilars in their therapeutic area (n = 73) prescribed biosimilars, while 40% didn't Concerns: 81% efficacy in extrapolated indications, 81% immunogenicity, 79% efficacy, 78% safety, 73% quality and 62% traceability	67% of medical specialists that prescribed biosimilars (n = 43) would most likely prescribe a biosimilar for treatment initiation	28% of medical specialists that prescribed biosimilars (n = 43) would be likely to switch from originator to biosimilar	<5% of medical specialists would consider pharmacist-led substitution appropriate

	E-mail-survey of 14-20 questions for 2917 physicians in national professional societies in 2016 (n = 253 analysed answers from general practitioners and n = 102 from medical specialists). Other stakeholders apart from physicians are not addressed in this review	35% familiar , and 6% and 25% had never heard the term "biosimilar"	the same as generic medicines 31% of medical specialists incorrectly agreed that biological medicines sharing the same international non-proprietary name were "structurally identical"	literature and 63% educational events GPs (n = 247, not all answered this question): 58% national or hospital formularies				49% consider decisions should be taken by the prescriber on treatment initiation and 61% during treatment course. 43% consider decisions should be agreed with clinician in advance on treatment initiation and 35% during treatment course 84% think notifications for physician very important or critical in treatment initiation and 90% during treatment course
O'Dolinar & Reilly 2014[25] (France, Germany, Italy, Spain and the United Kingdom)	Nephrologists', rheumatologists', dermatologists', neurologists', endocrinologists' and oncologists' attitudes on biosimilar naming, substitution, and knowledge, sources of information and need for further education on biosimilars Web-based 15-minutes short survey for 4,324 global physician market research panel of at the last quarter of 2013. 470 prescribers (20% of each five countries) completed the survey	46% responded having basic understanding, 43% complete understanding, 11% could not define biosimilars and 1% had never heard of biosimilars 53% incorrectly thought biosimilar and originator were structurally identical and 37% incorrectly believed biosimilars are clinically tested for all indications	N/A	47% conferences and seminars, 35% self-study, 11% studies sponsored by biosimilar companies and 6% equally studies sponsored by innovator companies, clinical trial participation and other routes	48% said it was very important, 24% critically important, 23% somewhat important, 4% slightly important and 1% not important to have a sole authority to select the medicine	47% considered that products with the same non-proprietary name could be safely given to a patient with same results, 40% didn't think that way	45% think patients can't be switched between the products with same non-proprietary names, 39% believed patients could be switched safely and effectively	62% not acceptable, 35% acceptable and 3% totally acceptable on pharmacist-led substitution 47% very important, 30% critical, 6% slightly important and 1% not important to receive a notification if the pharmacist had dispensed other than prescribed biologic medicine during a repeated treatment
van Overbeeke et al. 2017[26] (Belgium)	Knowledge and perceptions of patients and physicians with regard to originators and biosimilars and differences in perceptions and the factors influencing their preferences Web survey of multiple-choice and open-ended questions for all 232 Belgian rheumatologists in 2016 (n = 41 responded). Other stakeholders apart from physicians are not addressed in this review	95% considered biosimilars are similar, but not identical	90% were able to share the most complete definition of a biosimilar	N/A	7% had prescribed biosimilars. 73% preferred the originator when the prices were equal and 38% when originator was more expensive. When prices were equal, none preferred biosimilar. 93% considered price, 63% safety, 61% quality and 61% efficacy as sources of differences between originators and biosimilars 33% considered biosimilars and originators interchangeable if biosimilarity is proven in the same indication and 38% in indications where the medicine works via the same biological mechanism. 28% considered that biosimilars and originators were never interchangeable 56% think extrapolation could only be performed if efficacy and safety is proven to be similar in one of the indications and if the medicine works via the same mechanism in the other indications. 39% stated the indications should never be extrapolated Positive influencers: clinical trials with positive results and clinical data in the respective indication. Negative influencers: less studied than the originator and no clinical trials in the respective indication	8% would not prescribe a biosimilar and 60% would only prescribe a biosimilar to biologic-naïve patients.	N/A	N/A
Reilly & Murby 2017[34] (Australia)	Opinions on the naming of biologicals and biosimilars, how the use of these medicines is recorded and their views on substitution of, familiarity with, knowledge of, attitudes to and beliefs in biosimilars Web-based survey for prescribers recruited from a global, commercial database of health care professional in 2016 (n = 451, of which 160 completed the survey)	21% considered themselves very familiar and having complete understanding of biosimilars, 73% basic understanding and 6% could not define them	50% thought biosimilars go through the same regulatory process as original biologics 70% knew biosimilars could be approved for all or for some indications of the originator	46% published literature, 28% colleagues, 27% information from Pharmaceutical Benefits Advisory Committee, 24% product information label, 19% information from Therapeutic Goods Administration, 18% sales presentative, 13% hospital formulary 43% never used published literature	N/A	16% would be comfortable prescribing a biosimilar that was approved for several indications based on clinical trials in only one indication, 11% would not feel comfortable and 73% had some concerns on this	N/A	54% very and 36% critically important to have sole authority to decide of which biological was dispensed Evidence required for pharmacist-led substitution: 53% clinical trial data of no safety of efficacy risks in switching, 53% clinical trial data of no safety of efficacy risks after multiple switches, 27% in-market experience, 24% observational data and 6% no evidence would be sufficient
Sullivan et al. 2017[27] (Germany)	Motivators of prescribing biosimilars, preferences matching actual prescribing behaviour and patient	N/A	N/A	N/A	Biosimilars account for 12-13% of all biologic therapies the respondents prescribe	88% would prefer to prescribe originator to biosimilar as 1st line therapy	N/A	N/A

	acceptance, satisfaction and concerns on biosimilars and how these relate to the treatment with originators or biosimilars Real world, cross-sectional study (in which physicians filled a survey form and reported their prescribing, and recruited patients that also filled a questionnaire form to provide information on how reported prescribing was occurred in practice) in 2015-2016 (n = 25). Other stakeholders apart from physicians are not addressed in this review Based on their response, 11 physicians were assigned to investigative (primarily concerned with symptom improvement and disease modification), 7 to conservative (primarily concerned with safety) and 7 to other (influenced primarily by other factors)				Reasons to prescribe: desire to get experience with the new product (89% of investigative, 100% of conservative and 57% of other), being convinced of equivalent efficacy compared to originators (44%, 67% and 43%), lower cost (44%, 83% and 71%), believing that is economic prescribing (44%, 83% and 57%) and believing that using biosimilars makes savings which can be used elsewhere (22%, 67% and 29%)			
Waller et al. 2017[28] (Germany)	Motivators of prescribing biosimilars, preferences matching actual prescribing behaviour, and patient acceptance, satisfaction and concerns on biosimilars and how these relate to the treatment with originators or biosimilars Real world, cross-sectional study (in which physicians filled a survey form and reported their prescribing, and recruited patients that also filled a questionnaire form to provide information on how reported prescribing was occurred in practice) in 2015-2016 (n = 50). Other stakeholders apart from physicians are not addressed in this review Based on their response, 23 physicians were assigned to investigative (primarily concerned with symptom improvement and disease modification), 17 to conservative (primarily concerned with safety) and 10 to other (influenced primarily by other factors)	N/A	N/A	N/A	Biosimilars constitute less than 10% of the biologic therapies the respondents prescribed Reasons to prescribe: desire to get experience with the new product (86% of investigative, 65% of conservative and 50% of other), being convinced of equivalent efficacy compared to originators (64%, 65% and 50%) and lower costs (64%, 71% and 88%)	>95% would prefer to prescribe originator to biosimilar as 1st line therapy	N/A	N/A

Physicians use several information sources on biologic medicines, such as scientific publications (25–84%), self-study (35–84%), pharmaceutical companies (32–76%), guidelines from professional societies (26–75%), educational events and conferences (17–71%), other published literature (46–68%), physician colleagues (28–54%), safety registries (52%) and pharmacist colleagues (19%)[10, 16, 18, 21, 23-25, 29-30, 33-34, 36] (**Table 2**). According to a single study and a systematic literature review, information sources may vary according to the educational background of physicians, as the most common information source were the guidelines from professional societies for medical specialists and the national or hospital formularies for general practitioners[10, 33].

Table 3. Summary of the quality evaluation of the 23 included studies of this systematic review.

Reference	Main strengths	Main limitations	Quality according to the quality assessment protocol
Aladul et al. 2019[17]	Results logically and clearly displayed	Details of the questionnaire form were not available, discussion on methodology partly lacking	High
Baji et al. 2016a[19]	Well-described and logically presented methodology, results and discussion	Ethical discussion lacking	High
Baji et al. 2016b[20]	Well-described and logically presented methodology, results and discussion	Critical and ethical discussion partly lacking	High
Chapman et al. 2018[22]	Mainly well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
Grabowski et al. 2015[32]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High*
Hemmington et al. 2017[35]	Well-described and logically presented methodology, results and discussion	Details of the questionnaire form were not available, more in-depth information could have been collected by a qualitative study	High
Leonard et al. 2019[33]	Systematic approach with well-described methodology, results and discussion	Quality assessment of publications selected for systematic review is lacking, data not extracted study by study basis, no two reviewers in all steps of the systematic literature review process	High
O'Callaghan et al. 2017[10]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
van Overbeeke et al. 2017[26]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
Aladul et al. 2018[18]	Semi-structured interviews provide a more in-depth view on the perceptions of healthcare professional in comparison to short surveys	Exact numbers of respondents which certain opinion (n) not always reported, low number of representatives per each professional group	Moderate*
Barsell et al. 2017[29]	Well-presented results and discussion	Details of the questionnaire form were not available, description of methodology lacking, e.g. dropout not described, ethical discussion lacking	Moderate
Beck et al. 2016[21]	Well-presented results and discussion	Details of the questionnaire form were not available, validity of the instrument unclear, as more in-depth information could have been collected by a qualitative study, dropout not described accurately	Moderate*
Sullivan et al. 2017[27]	Results clearly presented	Dropout not described accurately, some inconsistencies in the presentation of methodology and discussion	Moderate*
Waller et al. 2017[28]	Well-presented results and discussion	Some inconsistencies in the presentation of methodology, e.g. sample selection and dropout	Moderate*
Akhmetov et al. 2015[16]	Explicit aims	Clear presentation of results lacking, critical and ethical discussion lacking	Low
Cohen et al. 2016[30]	Mainly well-presented results and discussion	Details of the questionnaire form were not available, description of methodology lacking, ethical discussion lacking	Low
Danese et al. 2016[23]	Results clearly presented	Details of the questionnaire form were not available, critical and ethical discussion partly lacking, description of methodology partly lacking	Low
Danese et al. 2014[24]	Results clearly presented	Statistical analyses lacking, critical and ethical discussion lacking, description of methodology partly lacking, for example the number of invited members not mentioned	Low
Farhat et al. 2016[37]	Mainly logically presented methodology	Aim is not explicitly presented, number of physicians who responded not reported, results presented in table format only, critical discussion lacking	Low*
Felix et al. 2014[31]	Explicit aims	Strategic sample selection, details of the questionnaire form were not available, exact numbers of respondents which certain opinion (n) not always reported, description of used statistical methods and data analysis lacking, inconsistency in the description of results	Low
Gewanter & Reilly 2014[36]	Explicit aims	Respondents from market research panel resulting that respondents work in disciplines in which don't necessarily involve biosimilars, such as psychiatry, description of used statistical methods and data analysis lacking, critical and ethical discussion lacking	Low
O'Dolinar & Reilly 2014[25]	Explicit aims	Intentional sample selection, clear presentation of results lacking, critical and ethical discussion lacking	Low
Reilly & Murby 2017[34]	Explicit aims	Description of data collection partly lacking, description of used statistical methods and data analysis lacking	Low

* Differences in opinions of which quality grade each publication was given, set in consensus

Attitudes towards and experienced advantages and disadvantages of biosimilars (n = 22)

Physicians' reported attitudes towards biosimilars seem contradictory[10, 19-24, 26-32, 35-37] (**Table 2**). Some (6–38%) physicians consider biosimilars and originator products interchangeable, while others (28%) never think so[24, 26]. Some studies show that 65–67% of physicians have concerns regarding biosimilars[19-20], while others report that 54–94% of physicians feel somewhat or very confident prescribing biosimilars[10, 21, 23, 32, 35]. Regardless, a positive attitude towards biosimilars does not automatically translate into prescribing, as physicians seem to prefer originator products to biosimilars[19, 26, 32]. Studies indicate that there might be differences in attitudes towards biosimilars between specialties: gastroenterologists seem frequent prescribers of biosimilars, while dermatologists and rheumatologists seem less enthusiastic[18, 22, 30].

The main experienced advantages of biosimilars are cost savings[17, 21-24, 29], lower price in comparison to the originator biologic medicine[29, 37] and physicians' willingness to try new treatments[27-28] (**Table 2**). Additionally, in single studies, robust pharmacovigilance studies[17], easier access to treatment for patients[29], and approval of the European Medicines Agency or the Food and Drug Administration[37] were reported as motivators for prescribing biosimilars. Most commonly reported disadvantages were distrust in safety[10, 17, 21, 29, 31, 33], efficacy[10, 17, 21, 29, 31, 33], immunogenicity[10, 24, 29, 33] and indication extrapolation of biosimilars[10, 32-33] or the lack of clinical data on biosimilars[23, 33, 35]. Single studies also suggested the quality[10], traceability[10] or tolerability[21] of biosimilars and patients' concerns towards biosimilars[21] as disadvantages.

Initiation of biosimilars and switches between original biologic medicines and biosimilars (n = 22)

Physicians (39–89%) seem more eager to prescribe a biosimilar for biologic-naïve patients rather than patients already treated with biologic medicines[10, 19-, 22, 24, 26-29, 31-37] (**Table 2**). In discrete choice experiment studies, for example, 61–84% of gastroenterologists chose biosimilars in at least one of the choice sets for biological-naïve patients[19-20]. However, there are also other factors affecting the medicine selection, such as the cost of the medicines. It was reported, that if cost were not an issue, only 11% of physicians would choose a biosimilar for treatment initiation[32]. Additionally, studies suggest that some personal characteristics may influence on the uptake of biosimilars by individual physicians. Men, senior consultants and those treating more patients[20], along with those with greater familiarity with brand name medicines and uncertainty of long-term safety of biosimilars[32] were often unlikely to choose a biosimilar as initial therapy. Within medical specialties, gastroenterologists (95% with no concerns) appear most confident to use biosimilars in treatment initiations, followed by rheumatologists (92%), dermatologists (79%) and diabetologists (75%)[22].

Physicians did not seem eager to switch an originator biologic medicine to a biosimilar[10, 19-24, 30-32, 35-36] (**Table 2**). The share of physicians that were willing to switch an originator to a biosimilar was 51 % or less with the exception of a single study in which the percentage was 91%[10, 21, 23-24, 30, 32, 35]. Similarly, when it comes to treatment initiation, medical specialty of the individual physician effects his or her willingness to switch biologic medicines[22]. Gastroenterologists (95% with no concerns) seem most confident on switching, followed by dermatologists (78%), diabetologists (69%) and, notably, rheumatologists (53%).

Pharmacist-led substitution of biologic medicines (n = 10)

Physicians (64–95%) are concerned about or disagree with pharmacist-led substitution of biologic medicines[10, 18, 21, 23-25, 29, 32-34] (**Table 2**). Studies suggest that having full autonomy on medicine selection and being fully aware of which medicines their patient receives, was often crucial for physicians[10, 25, 29, 34]. However, according to a single study, 88% of physicians believe that there will be a political change resulting to pharmacist-led substitution without consulting physicians in the future[29].

4 DISCUSSION

According to this systematic review, physicians' knowledge on biosimilars varies widely. In general, measured knowledge appears weaker than self-assessed knowledge. Physicians use multiple information sources on biologic medicines, most commonly scientific publications, pharmaceutical companies and professional societies. Similar to their knowledge, physicians' perceptions towards biosimilars and the uptake of these medicines also vary. Physicians seem to prefer originator products to biosimilars and prescribe biosimilars mainly for biologic-naïve patients. Physicians consider cost savings and lower price in comparison to the originator biologic medicine as main advantages of biosimilars, while doubts often relate to safety, efficacy and immunogenicity of biosimilars. Most physicians have negative perceptions towards pharmacist-led substitution of biologic medicines.

Physicians' knowledge on biosimilars

This study found that physicians' knowledge on biosimilars appears inadequate. This may contribute to low prescribing and uptake of biosimilars[10, 30, 33]. Although this issue has been widely recognised, there is limited evidence on the effectiveness of education interventions on prescribing[39]. On the contrary, academic detailing has proven to be effective in steering prescribing[40-41]. Academic detailing is a method in which a trained educator meets with a healthcare professional and shares the latest evidence-based information on the topic that is educated[42]. Besides its' effectiveness in steering prescribing patterns, academic detailing has been proven to improve the cost-effectiveness of prescribing and reduce medical costs[43-44]. It is vital that in the near future physicians and other healthcare professionals are provided targeted, evidence-based information on biosimilars to support their uptake and to gain the full cost-saving potential of these medicines[45-46]. The educational efforts from medical societies is also vital in the distribution of appropriate biosimilar information[11].

Physicians' attitudes towards biosimilars and means to enhance the uptake

According to this study, physicians' attitudes towards biosimilars are contradictory and the prescribing of biosimilars is more often directed to biologic-naïve patients. This is despite of convincing evidence that supports switching[47]. Prescribing decisions can either be made by individual physicians or, if thereafter necessary, they can be steered by binding policies that vary across countries. Furthermore, besides actual steering policies, there are general differences across health systems in prescribing, dispensing, pricing and reimbursement of biologic medicines that may effect on the uptake. [10-11]. For example in Denmark and Norway, hospital, regional or national tendering is in use, resulting in significant savings in the purchase of biologic medicines[11, 48-49]. Some countries have implemented incentives for healthcare professionals[11]. Prescription quotas that define the ratio of biosimilars of all prescribed biologic medicines, are in use in Germany and Sweden[50], while gain-sharing agreements that enable using the savings from biosimilar uptake to be used in the benefit of the clinic or the organisation are used in Sweden and in the United Kingdom[51-52]. Pharmacist-led substitution of biologic medicines can also be seen as a potential mean to enhance the uptake of biosimilars[11, 29]. Pharmacist-led substitution is legislatively possible in France and in the United States, and for some biological medicines in Australia[53-55]. Furthermore, the implementation of pharmacist-led substitution is currently ongoing in some European countries[45, 56]. All these initiatives highlight that the weak uptake of biosimilars has been acknowledged globally, and there is a need to discover sustainable means to enhance and stabilize their uptake[11]. What complicates the issue is that, for example in Europe, even though the biosimilarity between biologic medicines is stated by the European Medicines Agency, the decisions on the interchangeability and substitution are made at the national level. In order to support the uptake of biosimilars, educational measures for both healthcare professionals and patients are needed, although the role of national recommendations, policies and steering for switching and substitution of biologic medicines should not be understated[29, 45-46].

Strengths and limitations

To the authors' knowledge, systematic reviews solely on the physicians' perceptions towards the uptake of biosimilars have not been published prior to this review. However, the results of this review are in line with an earlier systematic review on healthcare providers' perceptions on biosimilars[33]. Notable points on the earlier review on healthcare providers' perceptions, that were improved for this review, were that no quality assessment of included studies was conducted in the previous review, there was only one reviewer screening full texts for inclusion, and that the data was not separately extracted study-by-study basis. Thus, this review provides novel information on the topic with more systematic approach. In addition, main strengths of our review are that the literature search was conducted with the help of an experienced information specialist, and the quality evaluation of studies was conducted independently by two researchers in order to avoid bias[57]. Whereas one major limitation of this review was that the study-by-study data extraction was only done by one researcher. Furthermore, theses or reports by authorities that could have included research results were excluded from this study. In addition, any of the available protocols for quality assessment did not cover different types of study settings and the protocol used in this study was compiled from four separate protocols. In addition, included studies were conducted in different countries with unique regulatory laws and policies that undoubtedly effect on the uptake and prescribing of biosimilars in the national level. Regardless, it is vital to compile studies from different countries with different systems and policies in order to form a comprehensive view on the current situation on the uptake of biosimilars. One notable point is also that the data in the studies that were included in this review were mainly collected in 2017 or before. The topic is very timely and perceptions towards the uptake of biosimilars may change according to new research information, interventions and experience in using these medicines. Thus, there is a need to continue examining perceptions of physicians, both in general and with different disciplines, particularly with qualitative research methods. Further studies are needed to explore the differences between disciplines in the attitudes towards and prescribing of biosimilars as the reasons behind these differences were not possible to explore in detail based on the studies included in this review.

Practical implications

This systematic review provides up-to-date knowledge on the physicians' perceptions on the uptake of biosimilars and highlights the need for further education and steering upon this issue. The knowledge provided by the review may be utilised in visioning future means to enhance the uptake of biosimilars that could include information sharing and educational interventions by means of e.g. academic detailing. Uptake of biosimilars may also be enhanced by implementing national policies or steering procedures to support the uptake, by means of pharmacist-led substitution of biologic medicines, for example.

5 CONCLUSIONS

This systematic review concludes that physicians' knowledge on and attitudes towards biosimilars vary. Although physicians have positive attitudes towards biosimilars, prescribing is limited, especially for patients that are already treated with biologic medicines. Perceptions towards the pharmacist-led substitution of biologic medicines are often negative. Education and national recommendations and policies for switching and substitution of biologic medicines are needed to support the uptake of biosimilars.

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COMPETING INTERESTS

Authors declare no competing interests.

AUTHOR'S CONTRIBUTIONS

KS, MM, JJ and KHA contributed to the conception or study design. KS and MM acted as principal investigators in the search and evaluation of the literature and in the quality assessment. KS drafted the manuscript. All authors participated in critical revision of the manuscript and approved the final version.

PATIENT CONSENT

Not required.

ETHICAL CONSENT

Not required.

PATIENT AND PUBLIC INVOLVEMENT

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

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FIGURE LEGENDS

Figure 1. PRISMA flow chart explaining the study inclusion process.

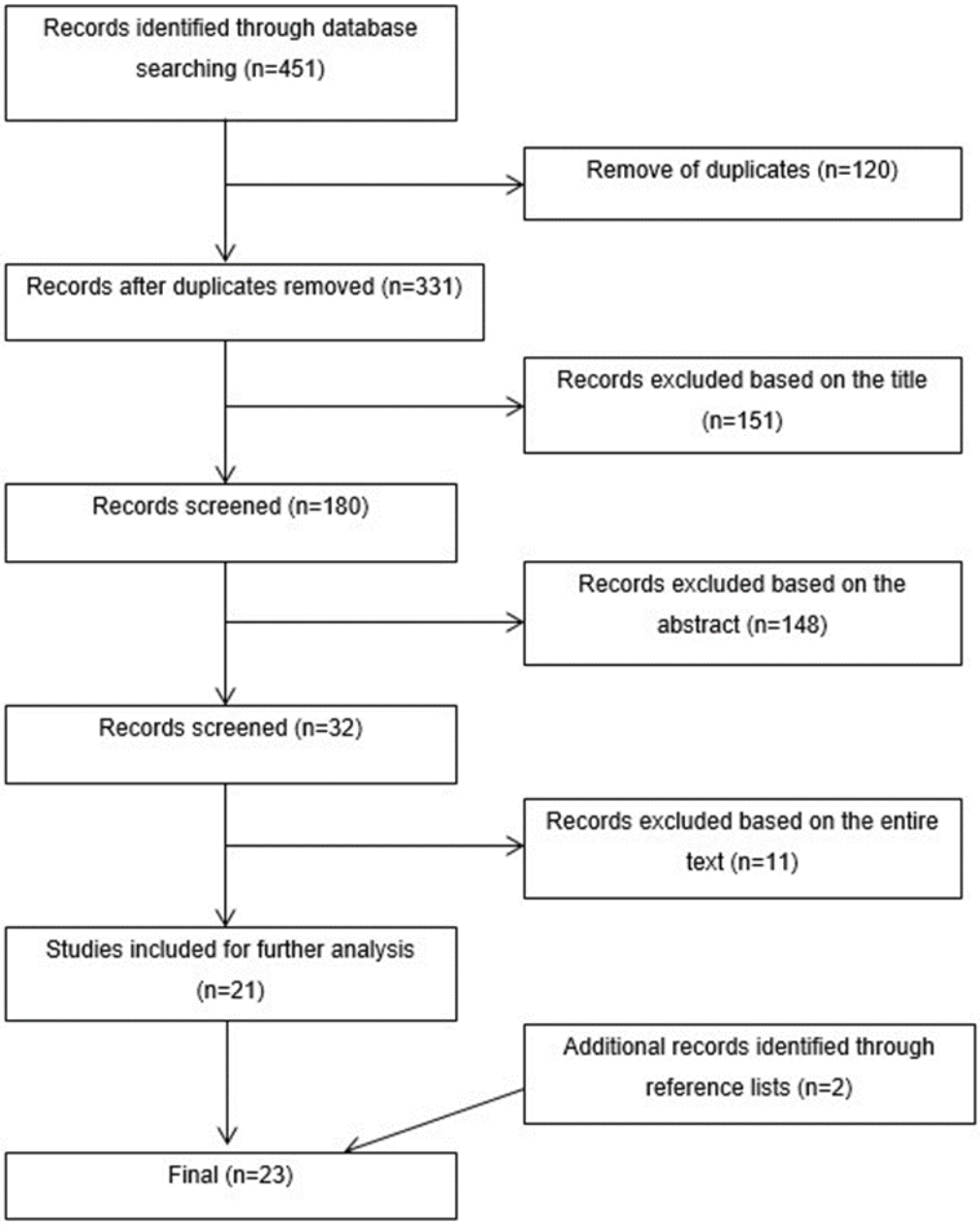

Figure 1. PRISMA flow chart explaining the study inclusion process.

Appendix 1. Literature search approach.

Database	Search terms
MedLine Ovid	(attitude* or stance* or opinion* or position* or orientat* or insight* or esteem* or estimat* or percepti* or belie* or decision* or decide* or determin* or prescrib* or chose* or choos* or choice* or guid* or recommend* or commission* or adopt* or accept* or uptak* best practice).mp AND (((physician.mp. or Physicians/) OR (clinician* or doctor* or specialist* or consultant*).mp.) AND (exp dermatology/ or exp internal medicine/ or exp endocrinology/ or exp gastroenterology/ or exp rheumatology/)) OR (exp general practice/ or exp family practice/ or exp general practitioners/ or exp hospitalists/ or exp physicians, family/ or exp physicians, primary care/or physician.mp. or Physicians/ or (clinician* or doctor* or specialist* or consultant*).mp.) AND (exp DIABETES MELLITUS/ or diabetes.mp.)) AND (exp Biosimilar Pharmaceuticals/ or biosimilar*.mp.) (attitude* or stance* or opinion* or position* or orientat* or insight* or esteem* or estimat* or percepti* or belie* or decision* or decide* or determin* or prescrib* or chose* or choos* or choice* or guid* or recommend* or commission* or adopt* or accept* or uptak* best practice).mp AND (((Physicians/ or (physician* or clinician* or doctor* or specialist* or consultant*).mp.) AND (exp Biosimilar Pharmaceuticals/ or biosimilar*.mp.)
Scopus	TITLE-ABS-KEY (biosimilar* AND (((physician* OR clinician* OR doctor* OR specialist* OR consultant*) W/20 (rheumatology OR gastroenterology OR endocrinology OR dermatology OR diabetes OR "internal medicine")) OR (rheumatologist* OR gastroenterologist* OR endocrinologist* OR dermatologist* OR hospitalist OR "General Practitioner*" OR physicians W/2 family)) AND (attitude* OR stance* OR opinion* OR position* OR orientat* OR insight* OR esteem* OR estimat* OR percepti* OR belie* OR decision* OR decide* OR determin* OR prescrib* OR choice* OR choos* OR chose* OR "best practice" OR guidi* OR guide* OR recommend* OR commission* OR adopt* OR accept* OR uptak*)) AND (LIMIT-TO (SRCTYPE , "j ") OR LIMIT-TO (SRCTYPE , "p ")) AND (LIMIT-TO (DOCTYPE , "ar ") OR LIMIT-TO (DOCTYPE , "re ") OR LIMIT-TO (DOCTYPE , "cp ") OR LIMIT-TO (DOCTYPE , "ip ")) AND (LIMIT-TO (LANGUAGE , "English ")) TITLE-ABS-KEY(biosimilar* AND (physician* OR clinician* OR doctor* OR specialist* OR consultant*) AND (attitude* OR stance* OR opinion* OR position* OR orientat* OR insight* OR esteem* OR estimat* OR percepti* OR belie* OR decision* OR decide* OR determin* OR prescrib* OR choice* OR choos* OR chose* OR "best practice" OR guidi* OR guide* OR recommend* OR commission* OR adopt* OR accept* OR uptak*)) AND (LIMIT-TO (SRCTYPE,"j ") OR LIMIT-TO (SRCTYPE,"p ")) AND (LIMIT-TO (DOCTYPE,"ar ") OR LIMIT-TO (DOCTYPE,"re ") OR LIMIT-TO (DOCTYPE,"cp ") OR LIMIT-TO (DOCTYPE,"ip ")) AND (LIMIT-TO (LANGUAGE,"English "))

Appendix 2. Quality assessment protocol.

Date:

Evaluator:

Authors:

Title:

Design				**Yes**
Meta-analysis				
Randomized controlled trial				
Systematic review				
Quantitative study: type (survey, pilot, other)				
Qualitative study: type (interview, focus group, other)				
Other, what?				
	Yes (1p)	**Partly (½p)**	**No (0p)**	**Notes**
Aim and context				
1 Is there an explicit aim?				
2 Is the context described?				
Methodology				
3 Is the data collection described accurately and is it repeatable?				
4 Is the sample selection preventative/relevant/not strategic (sample selected intentionally)?				
5 Is the dropout described?				
6 Is the data analysis described accurately and is it repeatable?				
7 Are the (statistical or other) methods adequate and applicable in relation to the aims of the study?				
Results				
8 Are the findings logic, reliable and clearly displayed?				
Discussion and conclusions				
9 Is there a critical discussion on the findings?				
10 Is there a critical discussion on the method?				
11 Is there a new value?				
12 Are the aims of the study met in the results and findings of the study?				
13 Are the instruments valid?				
14 Are the instruments reliable?				
Ethics				
15 Is there an ethical discussion?				
16 Are the authors non-dependable and free of any conflicts of interest?				
17 Did the participants participate without receiving a fee?				
TOTAL POINTS				

Quality assessment (rounded upwards when necessary): high: ≥ 15 yes, moderate: 12-14.5 yes, low: < 12 yes

Quality assessment protocol adapted from the protocols of Åkesson et al. (2006), Tong et al. (2007), Joanna Briggs Institute (2014) and Swedish Agency for Health Technology Assessment and Assessment of Social Services (2016).

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on section (in the main document without
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page, p1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Title page, p1, according to BMJ Open abstract structure
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, starting from p2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Objectives (at the last paragraph of the Introduction), p2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Material and methods, paragraph: Quality assessment, with an appendix and appropriate referencing, p3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Tables 1 and 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Appendix 1 in the Supplementary Files
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1 in the Supplementary Files
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Material and methods: Literature search, p2–3 and Table 1, p3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Material and methods: Data extraction and analysis, p3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Material and methods: Data extraction and analysis, p3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Material and methods: Quality assessment, p3 and Table 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on section
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results: Quality assessment, Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, p14 onwards, Tables 2 and 3
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, p14 onwards
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusions, p14 onwards
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding, p15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Physicians' perceptions on the uptake of biosimilars - A systematic review

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Primary Subject Heading:	Health policy
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Keywords:	biosimilar, biologic medicine, physician, perception

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1

Physicians' perceptions on the uptake of biosimilars - A systematic review

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ABSTRACT

Objectives: Examine physicians' perceptions on the uptake of biosimilars

Design: Systematic review

Setting: Literature search in MedLine Ovid and Scopus databases at the end of 2018. Search resulted to 451 studies and after removal of duplicates, to 331 studies. Two researchers examined studies based on the title, abstract and the entire text. Twenty scientific original studies written in English that addressed physicians' perceptions on the uptake of biosimilars were selected for further analysis. Additionally, the references of included studies were screened and three studies were handpicked and included in this review. Data of these 23 studies were extracted study-by-study basis. All publications were quality assessed by two researchers. In this review, higher emphasis was given to publications with high-assessed quality.

Results: Majority of selected studies were conducted in Europe and they commonly utilized short surveys. Physicians' familiarity of biosimilars varied: 49–76% were familiar with biosimilars and 2–25% did not know what biosimilars were, percentages varying from study to study. Measured knowledge appeared weaker compared to self-assessed knowledge. Physicians' perceptions towards biosimilars also varied: 54–94% were confident prescribing biosimilars, while 65–67% had concerns regarding these medicines. Physicians seem to prefer originator products to biosimilars and prescribe biosimilars mainly for biologic-naïve patients. Physicians consider cost savings and lower price in comparison to the originator biologic medicine as main advantages of biosimilars, while doubts often relate to safety, efficacy and immunogenicity. 64–95% of physicians have negative perceptions towards pharmacist-led substitution of biologic medicines.

Conclusions: Physicians' knowledge on and attitudes towards biosimilars vary. Although physicians had positive attitudes towards biosimilars, prescribing is limited, especially for patients that are already treated with biologic medicines. Perceptions towards the pharmacist-led substitution of biologic medicines are often negative. Education and national recommendations for switching and substitution of biologic medicines are needed to support the uptake of biosimilars.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first systematic review conducted solely on physicians' perceptions regarding the uptake of biosimilars
- The literature search was conducted with the help of an experienced information specialist
- Publications selected for this review were quality evaluated by two researchers independently
- The quality evaluation protocol was compiled from four existing evaluation protocols
- The data in the studies included in this review was mainly collected before

KEYWORDS

biosimilar, biologic medicine, physician, perception, systematic review

1 INTRODUCTION

Biologic medicines consist of one or multiple biologic active substances and are often manufactured through biotechnology[1-2]. Biologic medicines were first developed mainly for rare diseases, but have thereafter improved the treatment of many common diseases, such as diabetes, arthritis and psoriasis[1]. The flipside of this transformation are high costs of biologic medicines that have contributed to increased medical costs globally[3].

Biosimilars are biologic medicines highly similar to the originator biologic medicines with same standards on the quality, safety and efficacy of the products[2-4]. Biosimilars have no clinically meaningful differences to the existing reference product. Biosimilars are not regarded as generic medicines due to the complex manufacturing process and the natural variability between manufacturing batches of biologic medicines. The comparability of the product to the reference product has to be demonstrated, however, clinical trials are not required. As a result, biosimilars can be brought to the market at a lower cost in comparison to the originator biologic product. The uptake of biosimilars could lead to healthcare cost savings and better patient access to costly biologic therapies[5]. Until the end of 2018, 50 biosimilars have received marketing authorisation in Europe and 15 in the United States[6-7].

Regardless of their demonstrated comparability and their cost-saving potential, biosimilars have not fully penetrated the market of biologic medicines. The European Union holds 80% of the global biosimilar market, but biosimilars constitute only 1% of total sales of biologic medicines[8-9]. It has been stated that the decisions to select biologic medicines may be either policy driven or made by individual physicians, which has raised a need to assess the prescribing of biosimilars in a critical manner[10-11]. Physicians' reluctance to prescribe biosimilars may restrain potential savings in medical costs that could enable offering biologic treatment to larger patient populations and providing more cost-effective treatment, as similar benefits could be gained by using less expensive treatments. Therefore, it is vital to study physicians' attitudes towards and perceptions on the uptake of biosimilars. Published information on the topic is somewhat contradictory. A previous systematic review focused on health care providers' knowledge, perceptions and prescribing behaviors of biosimilar medicines[12]. As the role of physicians is critical in the uptake of biosimilars and gaining the cost-saving potential, a wider understanding on physicians' perceptions on the uptake of biosimilars with a critical quality evaluation of the published literature was needed. Thus, the aim of this systematic review was to examine physicians' perceptions on the uptake of biosimilars.

2 MATERIAL AND METHODS

Literature search

A systematic literature search was conducted in MedLine Ovid and Scopus databases at the end of 2018. Selected databases provide a comprehensive selection of scientific publications from the disciplines of pharmacy and medicine. The systematic search strategy (**Appendix 1**) was constructed by the research group and the search was conducted by an experienced information specialist.

The initial search resulted in 451 studies. After removal of duplicates (n = 120), 331 studies remained. Studies were examined based on the title, abstract and the entire text by two researchers independently (KS and MM). Of the 331 studies, 152 were excluded based on the title, 148 based on the abstract and 11 based on the entire text. At each stage, researchers shared their views of the studies, discussed on possible differences on opinions and

reached a consensus opinion based on the discussion. The inclusion and exclusion criteria of this systematic review are presented in **Table 1**. A total of 20 publications were selected for further analysis. Furthermore, the reference lists of these 21 articles were screened and three further articles that met the inclusion criteria were handpicked and included in this review, which brings the final number of included studies being 23. The PRISMA flow chart explaining the study inclusion process is presented in **Figure 1**.

Table 1. Inclusion and exclusion criteria of studies of this systematic review.

Inclusion criteria	Exclusion criteria
• Original primary studies	• Other than original primary studies, such as reviews, conference papers, consensus papers, commentaries and letters to editors
• English language	• Other language than English
• Investigating physicians' perceptions on the uptake of biosimilars (physicians in particular or at least 45% of physicians among other healthcare professionals, although only physicians perceptions were taken into account in this review)	• Investigating other healthcare professionals' perceptions on the uptake of biosimilars or publications with less than 45% of physicians of all participants involved or in which the physicians' perceptions are not separated in the results of the study
• Publications on the physicians' perceptions on the automatic substitution of biologic medicines	• Publications on the physicians' perceptions on the automatic or generic substitution of other medicines than biologics

Quality assessment

Each of the 23 selected studies was concisely reviewed. Quality assessment was conducted according to a protocol adapted from the protocols of Åkesson et al. (2006), Tong et al. (2007), Joanna Briggs Institute (2014) and Swedish Agency for Health Technology Assessment and Assessment of Social Services (2016)[13–16] (**Appendix 2**). Adapted protocol was developed and used in the quality evaluation, because the study designs of the included studies varied and there was no single protocol that was suitable for evaluating the studies in a consice manner. Two researchers conducted quality assessments individually and then compared their reviews. Differences in opinions (n = 6) were discussed and final evaluation was set in consensus. In the Results section of this systematic review, studies that were assessed as having high quality are emphasized in comparison to the results of those with moderate or low assessed quality.

Data extraction and analysis

A meta-analysis was not conducted due to the various methods and both qualitative and quantitative approaches applied in the studies that were included in this review. The following information was extracted from all included studies: general information (authors, year of publication, and country of publication), aims, methods and results. In regards to results, seven topics for data extraction were identified based on the topics discussed in the publications and on the discussion in the research group. These topics were: physicians' 1) self-rated knowledge of biosimilars, 2) measured knowledge on biosimilars, 3) information sources of biologic medicines, 4) attitudes towards and experienced advantages and disadvantages of biosimilars, 5) actions in the initiation of biosimilars for biologic-naïve patients, 6) actions in the switches between originators and biosimilars for patients already treated with biologic medicines and 7) thoughts on pharmacist-led substitution of biologic medicines. In the Results section of this systematic review, these seven topics are presented within four broader themes: physicians' 1) self-rated and measured knowledge on biosimilars and information sources on biologic medicines, 2) attitudes towards and experienced advantages and disadvantages of biosimilars, 3) perceptions on the treatment initiations with biosimilars and on the switches between originator biologic medicines and biosimilars and 4) attitudes towards

pharmacist-led substitution of biologic medicines. All percentages presented in the article refer to the percentages shown in the included studies of physicians with a certain opinion If more than one study investigated the topic, a range of persentages in these studies are shown.

3 RESULTS

Study characteristics

Physicians' perceptions on biosimilars have been studied mainly in Europe (n = 16)[10, 17–30] and North America (n = 4)[31–34]. Single studies have been conducted in Australia (n = 1)[35], New Zealand (n = 1)[36], Central and South America (n =1)[37] and in multiple African, European and Middle Eastern countries (n = 1)[38] (**Table 2**). All studies were published between 2014 and 2019, but majority of them (n = 20)[10, 17,20–22,24–34,35–38] in 2017 or before. The data presented in the studies were collected between 2013 and 2017. Most of the 23 selected publications utilized surveys, typically web-based questionnaires with 11–22 questions, or fully structured short interviews (n = 17)[10, 17–18,22–27,30–32,34,35–38]. In addition there was a qualitative interview study[19] and real-world cross-sectional studies (n = 2)[28–29], in which physicians filled a survey form and reported their prescribing and after, recruited patients that also filled a questionnaire form to provide information on how reported prescribing actualized in practice. There were also discrete choice method surveys (n = 2)[20–21], in which prescribers were given a hypothetical scenario and possible treatment options, and they were asked to choose the alternative they prefer[39]. Furthermore, one literature review with survey on the market uptake of biosimilars[33], has been conducted.

Quality assessment

Of 23 included studies, seven[10,18,20–21,23,27,34] were evaluated to be high, six[19,22,28–31]to be moderate and nine[17, 24-26,32–33,35,37–38] to be low in quality based on criteria used in this review (**Table 3**). Publications evaluated to be high in quality often included well-described and logically presented methods and results sections and a critical discussion section, of which those evaluated to be moderate or low quality typically lacked. In general, the quality assessment revealed that there is a lack of valid instruments and studies utilizing qualitative research methods.

Self-rated and measured knowledge on biosimilars and sources of information (n = 18)

There is variation on the physicians' self-rated knowledge on biosimilars (**Table 2**). In individual studies, physicians consider they have at least a basic understanding of the topic: 5–44% of the physicians reported that they feel very familiar and 49–76% that they feel familiar with biosimilars[10,24,26–27,31,34,35–36]. In these studies 2–25% of the physicians reported that they do not know what biosimilars are. In individual studies, physicians with more years of practice and those with specialisation consider themselves more familiar with biosimilars in comparison to less experienced colleagues and general practitioners[10, 22,34].

Although physicians self-rate that they generally feel familiar with biosimilars, the measured knowledge on the topic appears weaker (**Table 2**). 18–66% of the physicians incorrectly described biosimilars as generic medicines and 31–72% as structurally identical to originator medicines[10, 22–23,25,32,34–35,37–38]. However, in three studies, 76–100% of physicians were able to share the complete definition of a biosimilar correctly[18–19,27].

5

Table 2. Characteristics of the 23 studies included in this systematic review.

Reference (Country or region)	Aims and methods	Results						
		Self-rated knowledge	Measured knowledge	Information sources	Attitudes towards and experienced advantages and disadvantages of biosimilars	Initiation of biosimilars (biologic-naïve patients)	Switches between originators and biosimilars (patients already treated with biologicals)	Pharmacist-led substitution of biologic medicines
Akhmetov et al. 2015[17] (Ukraine)	Endocrinologists', oncologists', nephrologists', immunologists' and rheumatologists' awareness of biosimilars Short interviews with eight close-ended questions, including 6 Likert-type items (n = 82), time of the study not reported	Low to medium levels (not reported more specifically) of biosimilar awareness on a 1-5 scale, where 1=low and 5=high) Endocrinologists and nephrologists had higher levels of awareness than other respondents	N/A	Peer-reviewed journal articles (n = 35), internet (n = 31), medical conferences (n = 20), popular press (n = 9), key-opinion leaders (n = 3), drug manufacturers (n = 2)	On a 1-5 scale, likelihood of prescribing biosimilars: 68% average (specific numbers not reported), 23% below average and 9% above average Majority (n not reported) are likely to try biosimilars in small batches, and then gradually move to larger groups of patients, endocrinologists and nephrologists showing the greatest interest Facilitators of prescribing: 39% cost advantage, 22% certification of safety by EMA or FDA, 22% certification of efficacy by EMA or FDA, 10% propitiousness of the Cabinet of Ministers and 7% trust towards European, American and Japanese biotech companies as importers Majority (n not reported) required 40-50% lower price for biosimilars than original biologics, endocrinologists typically accepting 20-30% discount in comparison to rheumatologists and oncologists that anticipated over 50% discount	N/A	N/A	N/A
Aladul et al. 2019[18] (the United Kingdom)	Knowledge and attitudes of healthcare professionals (n = 150 dermatologists, diabetologists, gastroenterologists and rheumatologists) towards infliximab and insulin glargine biosimilars Web-based survey via selected medical associations between August 2016 and January 2017	80% were aware that biosimilars were available on their local formulary	76% correctly considered biosimilars as copies of originators	N/A	91% considered robust pharmacovigilance studies and 84% the costs as the most important influencer of their prescribing of biosimilars	22% had major concerns on the efficacy and 14% on the safety of biosimilars that prevented them of starting a biosimilar	50% had major concerns on the efficacy and 34% on the safety of biosimilars in the switches	N/A
Aladul et al. 2018[19] (the United Kingdom)	Perceptions of consultants with specialties of diabetes mellitus, ulcerative colitis, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis (n = 10) towards biosimilar infliximab, etanercept and insulin glargine and potential barriers and facilitators to their prescribing Semi-structured interviews of purposive convenience sample of West Midlands hospital staff between June-November 2017	N/A	All interviewees expressed an understanding of the concept of biosimilars and believed biosimilars were copies of originators	Conferences, pharmaceutical industry representatives, scientific journals and colleagues	Majority of rheumatologists and diabetologists (n not reported) would prescribe the reference product if the prices of the reference product and the biosimilar are equal Gastroenterologists expressed more confidence and fewer concerns than other specialists, stating that indication extrapolation had previously been the major obstacle in the biosimilar uptake, but that it had been overcome Majority of rheumatologists (n not reported) had concerns on indication extrapolation, considering their patients are very sensitive with higher multimorbid risks. Some rheumatologists (n not reported) openly declared being mistrustful on biosimilars Facilitators of prescribing were information from societies, authorities and national registries. Barriers of prescribing were unexpected adverse effects or increase in side effects, patients' reluctance on using biosimilars, complicated, unsuitable or non-user-friendly administration device, unavailability of dose strengths in comparison to originators	Majority (n not reported) were content to initiate biosimilars Minority of rheumatologists and diabetologists (n not reported) felt under pressure to initiate new patients with biosimilars by their organization Two rheumatologists were happier to initiate biosimilars rather than switching	All gastroenterologists (n = 7) and a minority of rheumatologists (n not reported) were content to switch patients from reference products to a biosimilar All those that were content with switching considered that patients should be given the choice between the products Majority of all physicians (n not reported) felt multiple switching based on cost reasons irrational	Majority (n not reported) has negative view on the pharmacist-led substitution of biologic medicines Minority (n not reported) considered that automatic substitution would be accepted in the next few years
Baji et al. 2016a[20] (Hungary)	Gastroenterologists' treatment preferences in ulcerative colitis Discrete choice experiment survey (in which prescribers are given hypothetical scenario and possible treatment options, and they are asked to choose the alternative they prefer[39]) in a Hungarian professional society meeting in 2014 (n = 51)	N/A	N/A	N/A	20% had no concerns on biosimilars, 67% had some concerns on efficacy and/or safety and 12% did not support the use of biosimilars due to the lack of RCT evidence	84% of all physicians and 80% of those who had some concerns (67%) chose biosimilar in at least one choice set The most important attribute driving the choice: stopping rule (whether treatment after 12 months is reimbursed) Estimated probability of choosing the originator over biosimilar in the present reimbursement situation: 48%. Probability of choosing the biosimilars with all the benefits offered over the originator in the present situation: 85% versus 15%	61% of all and 53% of those who were concerned chose biosimilar in at least one of the choice sets The most important attribute driving the choice: stopping rule Estimated probability of choosing the originator over biosimilar in the present reimbursement situation: 71%. Probability of choosing the biosimilars with all the benefits offered over the originator in the present situation: 63% versus 37%	N/A

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Baji et al. 2016b[21] (Hungary)	Gastroenterologists' treatment preferences in Crohn's disease Discrete choice experiment survey (in which prescribers are given hypothetical scenario and possible treatment options, and they are asked to choose the alternative they prefer[39]) in a Hungarian professional society meeting in 2014 (n = 51)	N/A	N/A	N/A	20% had no concerns on biosimilars, 65% had some concerns on efficacy and/or safety and 12% did not support the use of biosimilars due to the lack of RCT evidence Four clinicians were classified to "No biosimilar" attitude group, 19 to the "Biosimilar to new patients only" group and 27 to the "Biosimilar" group (one clinician was excluded from the analysis)	Men, senior consultants, working in inflammatory bowel disease centre and treating more patients were more likely to consider biosimilars for biologic-naïve patients only Estimated probability of choosing the originator over biosimilar, when no benefits are offered for using the biosimilar: 60%. Probability of choosing the biosimilar with all kinds of benefits over the originator: 89% versus 11% The most important attribute driving the choice: continuity of medicine supply	Estimated probability of choosing the originator over biosimilar, when no benefits are offered for using the biosimilar: 74%. Probability of choosing the biosimilar with all kinds of benefits over the originator: 44% versus 56% The most important determinant of choice: type of the treatment	N/A
Barsell et al. 2017[31] (USA)	Dermatologists' knowledge and perceptions of biosimilars, whether a practice gap exists and to study misconception and barriers to biosimilar usage Web survey of 14 multiple-choice questions for the members of five state dermatologic societies and National Psoriasis Foundation in 2015 (n = 97)	62% responded having basic understanding of biosimilars, 27% complete understanding and 11% that they have never heard of biosimilars	37% were aware that biosimilars are highly similar to the reference product, 26% described biosimilar as "generic", 27% described them as same bio-drug with equal bioequivalence and 10% said they did not know the definition. Those with complete understanding (27%), 21% incorrectly described biosimilar as "generic"	35% self-study, 25% scientific publications, 17% conferences and seminars, 3% biosimilar company-sponsored events and 20% other	Advantages: 71% low price to patients, 68% easier access to treatment and 65% low price to payers. Disadvantages: 71% efficacy, 66% potential switch to biosimilar without physicians' knowledge, 66% safety and 63% immunogenicity. 8% believed there were no advantages Convincing physicians of interchangeability: 44% extensive phase I, II and III studies, 37% valid longitudinal data from patient registries, 37% same level of testing (not specified more thoroughly) than generic medicines, 36% evidence of pharmacokinetic and pharmacodynamic equivalence	25% definitely or highly likely to prescribe a biosimilar 38% will try it on very selected patients	N/A	88% believed that there will be a political change resulting to pharmacist-led substitution without consulting physicians in the future 76% very important and 18% somewhat important to have control over whether patients receive originator or biosimilar
Beck et al. 2016[22] (France)	Knowledge, experience and opinions related to biosimilars and to identify expectations, barriers and possible options to promote prescription Web survey of 22 questions for nearly 500 rheumatologists in 2015 (n = 116)	55%/3% considered they had little/no knowledge of biosimilars 5% felt very well-informed Hospital-based rheumatologists were likely to be more familiar with biosimilars compared to office-based rheumatologists 98% had at least one question about biosimilars	85% thought biosimilars are similar to reference products that had gone off-patent; 85% considered biosimilars have no meaningful differences in quality, 80% in safety and 90% in efficacy; 65% thought that the assessment of biosimilarity requires more comprehensive data than generic drugs; and 46% believed that biosimilar marketing authorisation is granted on the sole investigation of pharmacokinetic bioequivalence	84% self-study and scientific publications, 76% pharmaceutical companies, 72% continuous training, 54% physician colleagues and 19% pharmacist colleagues	44% agree and 10% strongly agree being in favour of implementation of biosimilars Positive factors: 90% healthcare cost savings, 61% releasing of resources allowing treating additional patients, 49% positive impact on patients' access to innovative medicines and 46% health policy-makers incentives. Barriers: 67% indication extrapolation of efficacy and safety, 66% lack of information about tolerability, 59% risk of increasing patients' concerns, 57% lack of clinical trials and 55% patients' wishes to be treated with the originator	7% had already prescribed biosimilars mentioned in the survey 89% considered it was conceivable to start a treatment for biologic-naïve patients	25% could envision a switch	58% strongly disagree and 23% disagree of approving substitution by a pharmacist
Chapman et al. 2018[23] (the United Kingdom)	Healthcare professionals' knowledge and attitudes towards infliximab and insulin glargine biosimilars and factors influencing their prescribing and compare healthcare professionals' attitudes with the utilisation of these biosimilars in hospitals Web-based survey of 11 questions for societies of dermatology, diabetology, gastroenterology and rheumatology in 2016-2017 and drug utilisation analysis from DEFINE database in 2015-2016 (n = 234). Other stakeholders apart from physicians are not addressed in this review	N/A	72% correctly thought biosimilars are similar copies of biologic medicines, 18% thought biosimilars are generic biologic medicines, 3% counterfeit medicines, 3% had heard of them but did not know what they were, 3% had never heard of them and 1% new biological medicines 75% knew biosimilars were available on their local formulary	N/A	Gastroenterologists were most frequent prescribers of biosimilars (prescribing every day or week), followed by rheumatologists, diabetologists and dermatologists The dominant consideration: cost saving Increasing the use of biosimilars: regulatory guidance and robust pharmacovigilance studies, local policy, potential cost saving to organisation (whether or not savings were invested in the prescribers' department) and robust cost-effectiveness data of biosimilar vs. originator	95% and 90% of gastroenterologists, 92% of rheumatologists, 79% of dermatologists and 75% of diabetologists had no or minor concerns on safety 90% of gastroenterologists, 88% of rheumatologists, 74% of dermatologists and 68% of diabetologists had no or minor concerns on efficacy	95% of gastroenterologists, 53% of rheumatologists, 78% of dermatologists and 69% of diabetologists had no or minor concerns on safety 93% of gastroenterologists, 55% of rheumatologists, 79% of dermatologists and 65% of diabetologists had no or minor concerns on efficacy	N/A
Cohen et al. 2016[32] (USA)	Dermatologists', gastroenterologists', haematologist-oncologists', medical oncologists', nephrologists' and rheumatologists' awareness, knowledge, and	N/A	92% of dermatologists, 90% of gastroenterologists, 83% of rheumatologists, 74%	88% scientific journals, 73% FDA and 64% physician peers. Trust to media was less than 5%	Generally positive attitudes towards biosimilars. Dermatologists and rheumatologists appear less enthusiastic	N/A	91% open to switching patients to a biosimilar	N/A

	perceptions of biosimilars over time (survey will be repeated in 2-3 years) Survey of 19 questions in 2015-2016 (n = 1201)		of nephrologists, 69% of haematologist-oncologists and 63% of medical oncologists were aware which of the listed medicines in their specialty were biologic 56% of rheumatologists, 33% of gastroenterologists, 31% of dermatologists, 15% of nephrologists, 9% of medical-oncologists and 3% of haematologist-oncologists incorrectly reported there are no biosimilars available		62% considered the biosimilar will have equivalent efficacy as its originator and 57% that the biosimilar will be at least as safe as the originator 58% had concerns on patient compliance and access to treatments options with originators Positive factors: increased access and utilization of biologic medicines, expanded treatment options and provided savings for the healthcare system			
Danese et al. 2016[24] (Europe, countries not reported)	Evolution on thinking about biosimilars one year after they had become available in the EU. Comparison to the survey published by Danese et al. 2014[24] Web survey with 14 multiple-choice questions for members of European Crohn's and Colitis Organization in 2015 (n = 118)	56% judged that educational activities that they were exposed to was fair and adequate, while 16% found it unnecessary	N/A	More information was hoped from 75% medical societies, 52% multispecialty safety registries, 47% health institutions and 26% guidelines	29% totally confident, 18% very confident and 34% confident enough (5%, 8% and 26% in 2013) to prescribe a biosimilar Main advantage: 92% (90% in 2013) cost-sparing. Main issue: 42% the lack of data from clinical trials for all indications 27% (67% in 2013) consider biosimilars have higher immunogenicity compared to the originator and 17% (43% in 2013) different action than the originator 51% (24% in 2013) thought biosimilar should be approved for all the indications of the originator	N/A	44% (6% in 2013) would switch a patient with remission	89% (85% in 2013) disagreed with automatic substitution by a pharmacist 13% support substitution for new prescriptions and 13% for all patients
Danese et al. 2014[25] (Europe, countries not reported)	Awareness of and readiness to use biosimilars Web survey of 15 questions for 1,000 randomly selected European Crohn's and Colitis Organization members in 2013 (n = 307)	N/A	70% were aware that biosimilar is a similar copy, but not equal to the originator, 19% responded that it is a copy of biological agent, identical to the originator, like a generic	Preferred information: 81% multi-specialty international safety registries to monitor safety and effectiveness, 78% health institutions on the development of rules on the use of biosimilars, 66% medical societies, 61% data regarding the registration process for biosimilars and 57% multispecialty practice guidelines	6% thought that the originator and biosimilar were interchangeable The main advantage: cost-sparing (89%). The main issue: different immunogenicity pattern than the originator (67%) 50% agreed biosimilars can significantly reduce healthcare costs, 27% expected them only having a marginal impact, 6% expected additional costs of introduction, regulation and pharmacovigilance to offset any potential savings 24% agreed that the tested biosimilar could be approved for all indications of the originator in terms of safety and efficacy, 19% for all rheumatologic indications, 14% for the specific indication only, 3% stated that all biosimilars could be approved for all indications of the originator and 39% disagreed with all of the above	61% felt little or no confident in using biosimilars in their everyday clinical practice, 26% confident enough, 8% very confident, and 5% totally confident	28% would consider replacing originator with a biosimilar	64% against the substitution by pharmacist 18% would agree only for new patients
Farhat et al. 2016[38] (Algeria, Belgium, Egypt, Iran, Iraq, Italy, Jordan, Lebanon, Sudan and Syria)	Parameters on the acceptance and future prescription of biosimilars and worldwide situation focusing mainly on the EU and US laws, regulations and legislative pathways, pricing and challenging market access Survey for over 150 healthcare professional in the conference meeting in 2015 (n = 117 health care professionals responded, of which most were physicians; exact number of physicians who responded not reported). Other stakeholders apart from physicians are not addressed in this review	N/A	66% knew what biosimilars were, 12% did not know and 22% had not answered the question. Of those who knew (66%), 62% considered biosimilars bioequivalent to originator and have all preclinical and clinical trials equal to the originator 63% agreed that biosimilars are already marketed in the Arab and Middle Eastern markets, while 45% agreed that they are manufactured in the same region	N/A	Drivers for prescribing: 69% FDA or EMA approval, 65% lower price of bioequivalence in comparison to the originator, 48% bio-efficacy, 42% safety and 31% good manufacturing practices and high reputation of the manufacturer. 5% think biosimilars don't have advantages 35% considered the cost of treatment should not overcome its effectiveness or safety/tolerance 26% thought lower prices were good news as patients will be treated with biologics 27% consider biosimilars would bring cost savings 49% trust companies highly experienced in manufacturing small-molecule generic drugs and 55% companies with prior experience in manufacturing biologics as biosimilar producers	41% prescribe biosimilars while 33% don't (note that respondents were also other than physicians)	N/A	N/A
Felix et al. 2014[33] (USA)	Challenges and opportunities of market uptake of biosimilars from the perspectives of physicians and payers Survey for physicians that had written about or were familiar with biosimilars based on literature	N/A	N/A	N/A	Almost all physicians (n not reported) believed that if biosimilar was approved by FDA it will perform similarly to the originator with regard to safety and efficacy Influences of decision making: efficacy and safety, out-of-pocket costs to the patient, price of treatment and immunogenicity	Four physicians are somewhat likely, six very likely and three not likely to prescribe a biosimilar to a new patient	31%/61% (n not reported) say they are somewhat likely/very likely to switch an existing patient from originator to biosimilar	N/A

	review of Medline-indexed publications (n = 14). Other stakeholders apart from physicians are not addressed in this review				50% (n not reported) consider it is very important that there are proven chemical and pharmacokinetic similarities between originators and biosimilars Roughly half (n not reported) consider payer and cost considerations very important			
Gewanter & Reilly 2014[37] (Argentina, Brazil, Colombia and Mexico)	Understanding of biosimilars, how they use them and their concerns for the future Web-based survey for 6650 prescribers from global market research panel (n = 399)	35% did not consider themselves familiar with biosimilars, meaning they could not define them or had never heard of them	49% were aware of differences between biologicals, biosimilars and non-comparable biologicals. 30% were unaware that clinical trials for single indication lead to approval for multiple indications	71% seminars and conferences, 55% self-study, 32% education from biosimilar companies, 18% clinical trial participation and 4% other means 37% would like to learn from pharmaceutical companies	88% prescribe biologicals	50% said they believed if two biological medicines had the same non-proprietary scientific name, patient could receive either product and have the same result	44% said they believed if two biological medicines had the same non-proprietary scientific name, patient could be safely switched during a course of treatment, and the patient would have the same result 64% would not be comfortable switching for cost reasons rather medical reasons	N/A
Grabowski et al. 2015[34] (Canada)	Gaps in knowledge and attitudes towards biosimilars of rheumatologists Web-based survey of 29 questions for 369 members of Canadian Rheumatology Association in February 2014 (n = 81)	31% indicated themselves being familiar or very familiar with biosimilars Those with greater than 20 years of practice were significantly more likely to indicate themselves familiar or very familiar than those with 20 or less years of practice	66% considered biosimilars essentially same as generic drugs 38% were aware of Health Canada's guidance on clinical requirement for biosimilar approval	N/A	94% generally comfortable prescribing biologic medicines to their patients 31% comfortable prescribing biosimilars to their patients if biosimilar was currently available 29% declined until their colleagues recommend it 42% indicated a 30% price reduction, and a third a ≥50% price reduction being reasonable before payers mandated the use of biosimilars over brand name biologics 54% disagreed or strongly disagreed, 32% agreed or strongly agreed and 14% were neutral using biosimilars with extrapolated indications 49% not confident, 19% confident or very confident, and a third neutral on the long-term sustainability profile of the biosimilar with 30 weeks of head-to-head clinical trial	59% consider offering biosimilars, if biosimilar demonstrates that it is comparable to the brand name drug 72% unlikely or very unlikely, 11% likely or very likely and 16% neutral to offer a biosimilar, when biologic-naïve patient is an ideal candidate, where cost is not an issue Greater familiarity with established brand name drugs and uncertainty over the long-term safety of biosimilars were often cited among those unlikely or very unlikely offering biosimilars 54% did not typically prescribe a biosimilar, were likely or very likely to offer a biosimilar, when the provincial payer or insurance company mandated using a biosimilar	7.5% consider switching, if biosimilar demonstrates that it is comparable to the brand name drug	88% concerned or very concerned if a pharmacist had the ability to substitute a biologic drug for a biosimilar without the physician's approval
Hallersten et al. 2016[30] (France, Germany, Italy, Poland, Spain, Sweden, UK)	Preferences on type and detail of biosimilar information in Summaries of Product Characteristics (SmPC) and the use of information sources when prescribing biologics including biosimilars by dermatologists, endocrinologists, gastroenterologists, haematologists, nephrologists, oncologists and rheumatologists Web-survey with approx.. 30 multiple-choise questions for 210 physicians (30 from each of the country) who were members of panels of physicians (approximately 250-800 physicians per country) who agreed earlier to participate in such survey studies, in 2015	N/A	N/A	Frequently used information sources: 63% professional guidelines, 55% SmPCs, 51% peer reviewed journals, 42% national or hospital formularies The physicians preferred modified SmPC (modified for the purpose of the study) where additional information in the biosimilar label had been added, specifically: 1) clarifying which product (the biosimilar or the reference product) generated which clinical data, 2) inclusion of additional statements indicating that the product is a biosimilar, and 3) that similarity has been evaluated in preclinical and clinical studies.	N/A	N/A	N/A	N/A
Hemmington et al. 2017[36] (New Zealand)	Perceptions and attitudes towards efficacy, safety and manufacturing of biosimilars, factors associated with positive attitudes, indication extrapolation and switching, and circumstances in which physicians would be reluctant to prescribe biosimilars	76% reported being familiar and having basic understanding and 13% very familiar and complete understanding of biosimilars, 9% had heard of biosimilars,	N/A	N/A	70% very or somewhat confident of the efficacy of biosimilars Less than 20% had negative views Situations when biosimilars were not prescribed: 32% lack of clinical data, 17% evidence of adverse effects or lack of efficacy, 15% patients do well with current treatment and 6% patients have complex medical history	71% would prescribe biosimilars for all or some clinical conditions meeting the relevant criteria, 10% would do this for only few or no clinical situations	51% confident and 28% not very confident or not at all confident to switch patients	N/A

	E-mail survey for 327 physicians in medical specialist society (n = 110)	but could not define them, and 2% had never heard of biosimilars			47% very confident or somewhat confident, 32% not confident and the remainder undecided in indication extrapolation			
O'Callaghan et al. 2017[10] (Ireland)	Medical specialists', general practitioners' and community pharmacists awareness of and attitudes to biosimilars E-mail-survey of 14-20 questions for 2917 physicians in national professional societies in 2016 (n = 253 analysed answers from general practitioners and n = 102 from medical specialists). Other stakeholders apart from physicians are not addressed in this review	44% of medical specialists and 5% of general practitioners very familiar with biosimilars, 41% and 35% familiar , and 6% and 25% had never heard the term "biosimilar"	25% of medical specialists and 18% of general practitioners considered biosimilars the same as generic medicines 31% of medical specialists incorrectly agreed that biological medicines sharing the same international non-proprietary name were "structurally identical"	Medical specialists (n = 101, not all answered this question): 72% guidelines from professional societies, 68% published literature and 63% educational events GPs (n = 247, not all answered this question): 58% national or hospital formularies	59% of those aware of biosimilars in their therapeutic area (n = 73) prescribed biosimilars, while 40% didn't Concerns: 81% efficacy in extrapolated indications, 81% immunogenicity, 79% efficacy, 78% safety, 73% quality and 62% traceability	67% of medical specialists that prescribed biosimilars (n = 43) would most likely prescribe a biosimilar for treatment initiation	28% of medical specialists that prescribed biosimilars (n = 43) would be likely to switch from originator to biosimilar	<5% of medical specialists would consider pharmacist-led substitution appropriate 49% consider decisions should be taken by the prescriber on treatment initiation and 61% during treatment course. 43% consider decisions should be agreed with clinician in advance on treatment initiation and 35% during treatment course 84% think notifications for physician very important or critical in treatment initiation and 90% during treatment course
O'Dolinar & Reilly 2014[26] (France, Germany, Italy, Spain and the United Kingdom)	Nephrologists', rheumatologists', dermatologists', neurologists', endocrinologists' and oncologists' attitudes on biosimilar naming, substitution, and knowledge, sources of information and need for further education on biosimilars Web-based 15-minutes short survey for 4,324 global physician market research panel of at the last quarter of 2013. 470 prescribers (20% of each five countries) completed the survey	46% responded having basic understanding, 43% complete understanding, 11% could not define biosimilars and 1% had never heard of biosimilars 53% incorrectly thought biosimilar and originator were structurally identical and 37% incorrectly believed biosimilars are clinically tested for all indications	N/A	47% conferences and seminars, 35% self-study, 11% studies sponsored by biosimilar companies and 6% equally studies sponsored by innovator companies, clinical trial participation and other routes	48% said it was very important, 24% critically important, 23% somewhat important, 4% slightly important and 1% not important to have a sole authority to select the medicine	47% considered that products with the same non-proprietary name could be safely given to a patient with same results, 40% didn't think that way	45% think patients can't be switched between the products with same non-proprietary names, 39% believed patients could be switched safely and effectively	62% not acceptable, 35% acceptable and 3% totally acceptable on pharmacist-led substitution 47% very important, 30% critical, 6% slightly important and 1% not important to receive a notification if the pharmacist had dispensed other than prescribed biologic medicine during a repeated treatment
van Overbeeke et al. 2017[27] (Belgium)	Knowledge and perceptions of patients and physicians with regard to originators and biosimilars and differences in perceptions and the factors influencing their preferences Web survey of multiple-choice and open-ended questions for all 232 Belgian rheumatologists in 2016 (n = 41 responded). Other stakeholders apart from physicians are not addressed in this review	95% considered biosimilars are similar, but not identical	90% were able to share the most complete definition of a biosimilar	N/A	7% had prescribed biosimilars. 73% preferred the originator when the prices were equal and 38% when originator was more expensive. When prices were equal, none preferred biosimilar. 93% considered price, 63% safety, 61% quality and 61% efficacy as sources of differences between originators and biosimilars 33% considered biosimilars and originators interchangeable if biosimilarity is proven in the same indication and 38% in indications where the medicine works via the same biological mechanism. 28% considered that biosimilars and originators were never interchangeable 56% think extrapolation could only be performed if efficacy and safety is proven to be similar in one of the indications and if the medicine works via the same mechanism in the other indications. 39% stated the indications should never be extrapolated Positive influencers: clinical trials with positive results and clinical data in the respective indication. Negative influencers: less studied than the originator and no clinical trials in the respective indication	8% would not prescribe a biosimilar and 60% would only prescribe a biosimilar to biologic-naïve patients.	N/A	N/A
Reilly & Murby 2017[35] (Australia)	Opinions on the naming of biologicals and biosimilars, how the use of these medicines is recorded and their views on substitution of, familiarity with, knowledge of, attitudes to and beliefs in biosimilars Web-based survey for prescribers recruited from a global, commercial database of health care professional in 2016 (n = 451, of which 160 completed the survey)	21% considered themselves very familiar and having complete understanding of biosimilars, 73% basic understanding and 6% could not define them	50% thought biosimilars go through the same regulatory process as original biologics 70% knew biosimilars could be approved for all or for some indications of the originator	46% published literature, 28% colleagues, 27% information from Pharmaceutical Benefits Advisory Committee, 24% product information label, 19% information from Therapeutic Goods Administration, 18% sales presentative, 13% hospital formulary	N/A	16% would be comfortable prescribing a biosimilar that was approved for several indications based on clinical trials in only one indication, 11% would not feel comfortable and 73% had some concerns on this	N/A	54% very and 36% critically important to have sole authority to decide of which biological was dispensed Evidence required for pharmacist-led substitution: 53% clinical trial data of no safety of efficacy risks in switching, 53% clinical trial data of no safety of efficacy risks

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				43% never used published literature				after multiple switches, 27% in-market experience, 24% observational data and 6% no evidence would be sufficient
Sullivan et al. 2017[28] (Germany)	Motivators of prescribing biosimilars, preferences matching actual prescribing behaviour and patient acceptance, satisfaction and concerns on biosimilars and how these relate to the treatment with originators or biosimilars Real world, cross-sectional study (in which physicians filled a survey form and reported their prescribing, and recruited patients that also filled a questionnaire form to provide information on how reported prescribing was occurred in practice) in 2015-2016 (n = 25). Other stakeholders apart from physicians are not addressed in this review Based on their response, 11 physicians were assigned to investigative (primarily concerned with symptom improvement and disease modification), 7 to conservative (primarily concerned with safety) and 7 to other (influenced primarily by other factors)	N/A	N/A	N/A	Biosimilars account for 12-13% of all biologic therapies the respondents prescribe Reasons to prescribe: desire to get experience with the new product (89% of investigative, 100% of conservative and 57% of other), being convinced of equivalent efficacy compared to originators (44%, 67% and 43%), lower cost (44%, 83% and 71%), believing that is economic prescribing (44%, 83% and 57%) and believing that using biosimilars makes savings which can be used elsewhere (22%, 67% and 29%)	88% would prefer to prescribe originator to biosimilar as 1st line therapy	N/A	N/A
Waller et al. 2017[29] (Germany)	Motivators of prescribing biosimilars, preferences matching actual prescribing behaviour, and patient acceptance, satisfaction and concerns on biosimilars and how these relate to the treatment with originators or biosimilars Real world, cross-sectional study (in which physicians filled a survey form and reported their prescribing, and recruited patients that also filled a questionnaire form to provide information on how reported prescribing was occurred in practice) in 2015-2016 (n = 50). Other stakeholders apart from physicians are not addressed in this review Based on their response, 23 physicians were assigned to investigative (primarily concerned with symptom improvement and disease modification), 17 to conservative (primarily concerned with safety) and 10 to other (influenced primarily by other factors)	N/A	N/A	N/A	Biosimilars constitute less than 10% of the biologic therapies the respondents prescribed Reasons to prescribe: desire to get experience with the new product (86% of investigative, 65% of conservative and 50% of other), being convinced of equivalent efficacy compared to originators (64%, 65% and 50%) and lower costs (64%, 71% and 88%)	>95% would prefer to prescribe originator to biosimilar as 1st line therapy	N/A	N/A

Physicians use several information sources on biologic medicines, such as scientific publications (25–84%), self-study (35–84%), pharmaceutical companies (32–76%), guidelines from professional societies (26–75%), educational events and conferences (17–71%), other published literature (46–68%), physician colleagues (28–54%), safety registries (52%) and pharmacist colleagues (19%)[10,17,19,22,24–26,30–32,35,37] (**Table 2**). According to a single study, information sources may vary according to the educational background of physicians, as the most common information source were the guidelines from professional societies for medical specialists and the national or hospital formularies for general practitioners[10].

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Table 3. Summary of the quality evaluation of the 23 included studies of this systematic review.

Reference	Main strengths	Main limitations	Quality according to the quality assessment protocol
Aladul et al. 2019[18]	Results logically and clearly displayed	Details of the questionnaire form were not available, discussion on methodology partly lacking	High
Baji et al. 2016a[20]	Well-described and logically presented methodology, results and discussion	Ethical discussion lacking	High
Baji et al. 2016b[21]	Well-described and logically presented methodology, results and discussion	Critical and ethical discussion partly lacking	High
Chapman et al. 2018[23]	Mainly well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
Grabowski et al. 2015[34]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High*
Hemmington et al. 2017[36]	Well-described and logically presented methodology, results and discussion	Details of the questionnaire form were not available, more in-depth information could have been collected by a qualitative study	High
O'Callaghan et al. 2017[10]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
van Overbeeke et al. 2017[27]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
Aladul et al. 2018[19]	Semi-structured interviews provide a more in-depth view on the perceptions of healthcare professional in comparison to short surveys	Exact numbers of respondents which certain opinion (n) not always reported, low number of representatives per each professional group	Moderate*
Barsell et al. 2017[31]	Well-presented results and discussion	Details of the questionnaire form were not available, description of methodology lacking, e.g. dropout not described, ethical discussion lacking	Moderate
Beck et al. 2016[22]	Well-presented results and discussion	Details of the questionnaire form were not available, validity of the instrument unclear, as more in-depth information could have been collected by a qualitative study, dropout not described accurately	Moderate*
Hallersten et al. 2016[30]	Results clearly presented	Details of the panel of physicians in different European countries where the respondents were reqruited were not shown. Critical discussion on the method partly lacking.	Moderate
Sullivan et al. 2017[28]	Results clearly presented	Dropout not described accurately, some inconsistencies in the presentation of methodology and discussion	Moderate*
Waller et al. 2017[29]	Well-presented results and discussion	Some inconsistencies in the presentation of methodology, e.g. sample selection and dropout	Moderate*
Akhmetov et al. 2015[17]	Explicit aims	Clear presentation of results lacking, critical and ethical discussion lacking	Low
Cohen et al. 2016[32]	Mainly well-presented results and discussion	Details of the questionnaire form were not available, description of methodology lacking, ethical discussion lacking	Low
Danese et al. 2016[24]	Results clearly presented	Details of the questionnaire form were not available, critical and ethical discussion partly lacking, description of methodology partly lacking	Low
Danese et al. 2014[25]	Results clearly presented	Statistical analyses lacking, critical and ethical discussion lacking, description of methodology partly lacking, for example the number of invited members not mentioned	Low
Farhat et al. 2016[38]	Mainly logically presented methodology	Aim is not explicitly presented, number of physicians who responded not reported, results presented in table format only, critical discussion lacking	Low*
Felix et al. 2014[33]	Explicit aims	Strategic sample selection, details of the questionnaire form were not available, exact numbers of respondents which certain opinion (n) not always reported, description of used statistical methods and data analysis lacking, inconsistency in the description of results	Low
Gewanter & Reilly 2014[37]	Explicit aims	Respondents from market research panel resulting that respondents work in disciplines in which don't necessarily involve biosimilars, such as psychiatry, description of used statistical methods and data analysis lacking, critical and ethical discussion lacking	Low
O'Dolinar & Reilly 2014[26]	Explicit aims	Intentional sample selection, clear presentation of results lacking, critical and ethical discussion lacking	Low
Reilly & Murby 2017[35]	Explicit aims	Description of data collection partly lacking, description of used statistical methods and data analysis lacking	Low

* Differences in opinions of which quality grade each publication was given, set in consensus

Attitudes towards and experienced advantages and disadvantages of biosimilars (n = 21)

Physicians' reported attitudes towards biosimilars seem contradictory[10, 20–25,27–29,31–34,36–38] (**Table 2**). Some (6–38%) physicians consider biosimilars and originator products interchangeable, while others (28%) never think so[25, 27]. Some studies show that 65–67% of physicians have concerns regarding biosimilars[20–21], while others report that 54–94% of physicians feel somewhat or very confident prescribing biosimilars[10, 22,24,34,36]. Regardless, a positive attitude towards biosimilars does not automatically translate into prescribing, as physicians seem to prefer originator products to biosimilars[20,27,34]. Studies indicate that there might be differences in attitudes towards biosimilars between specialties: gastroenterologists seem frequent prescribers of biosimilars, while dermatologists and rheumatologists seem less enthusiastic[19,23,32].

The main experienced advantages of biosimilars are cost savings[18,22–25,31], lower price in comparison to the originator biologic medicine[31,38] and physicians' willingness to try new treatments[28–29](**Table 2**). Additionally, in single studies, robust pharmacovigilance studies[18], easier access to treatment for patients[31], and approval of the European Medicines Agency or the Food and Drug Administration[38] were reported as motivators for prescribing biosimilars. Most commonly reported disadvantages were distrust in safety[10,18,22,31,33], efficacy[10,18,22,31,33], immunogenicity[10,25,31] and indication extrapolation of biosimilars[10,34] or the lack of clinical data on biosimilars[24,26]. Single studies also suggested the quality[10], traceability[10] or tolerability[22] of biosimilars and patients' concerns towards biosimilars[22] as disadvantages.

Initiation of biosimilars and switches between original biologic medicines and biosimilars (n = 21)

Physicians (39–89%) seem more eager to prescribe a biosimilar for biologic-naïve patients rather than patients already treated with biologic medicines[10,20,23,25,27–29,31,33–38] (**Table 2**). In discrete choice experiment studies, for example, 61–84% of gastroenterologists chose biosimilars in at least one of the choice sets for biological-naïve patients[20–21]. However, there are also other factors affecting the medicine selection, such as the cost of the medicines. It was reported, that if cost were not an issue, only 11% of physicians would choose a biosimilar for treatment initiation[34]. Additionally, studies suggest that some personal characteristics may influence on the uptake of biosimilars by individual physicians. Men, senior consultants and those treating more patients[21], along with those with greater familiarity with brand name medicines and uncertainty of long-term safety of biosimilars[34] were often unlikely to choose a biosimilar as initial therapy. Within medical specialties, gastroenterologists (95% with no concerns) appear most confident to use biosimilars in treatment initiations, followed by rheumatologists (92%), dermatologists (79%) and diabetologists (75%)[23].

Physicians did not seem eager to switch an originator biologic medicine to a biosimilar[10,20–25,32–34,36–37] (**Table 2**). The share of physicians that were willing to switch an originator to a biosimilar was 51 % or less with the exception of a single study in which the percentage was 91%[10, 22,24–25,32,34,36]. Similarly, when it comes to treatment initiation, medical specialty of the individual physician effects his or her willingness to switch biologic medicines[23]. Gastroenterologists (95% with no concerns) seem most confident on switching, followed by dermatologists (78%), diabetologists (69%) and, notably, rheumatologists (53%).

Pharmacist-led substitution of biologic medicines (n = 9)

Physicians (64–95%) are concerned about or disagree with pharmacist-led substitution of biologic medicines[10, 19,22,24–26,31,34–35] (**Table 2**). Studies suggest that having full autonomy on medicine selection and being fully aware of which medicines their patient receives, was often crucial for physicians[10,26,31,35]. However, according to a single study, 88% of physicians believe that there will be a political change resulting to pharmacist-led substitution without consulting physicians in the future[31].

4 DISCUSSION

According to this systematic review, physicians' knowledge on biosimilars varies widely. In general, measured knowledge appears weaker than self-assessed knowledge. Physicians use multiple information sources on biologic medicines, most commonly scientific publications, pharmaceutical companies and professional societies. Similar to their knowledge, physicians' perceptions towards biosimilars and the uptake of these medicines also vary. Physicians seem to prefer originator products to biosimilars and prescribe biosimilars mainly for biologic-naïve patients. Physicians consider cost savings and lower price in comparison to the originator biologic medicine as main advantages of biosimilars, while doubts often relate to safety, efficacy and immunogenicity of biosimilars. Most physicians have negative perceptions towards pharmacist-led substitution of biologic medicines. The results in this review are in line with an earlier systematic review on healthcare providers' perceptions on biosimilars[12].

Physicians' knowledge on biosimilars

This study found that physicians' knowledge on biosimilars appears inadequate. This may contribute to low prescribing and uptake of biosimilars[10,12,32]. Although this issue has been widely recognised, there is limited evidence on the effectiveness of education interventions on prescribing[40]. On the contrary, academic detailing has proven to be effective in steering prescribing[41–42]. Academic detailing is a method in which a trained educator meets with a healthcare professional and shares the latest evidence-based information on the topic that is educated[43]. Besides its' effectiveness in steering prescribing patterns, academic detailing has been proven to improve the cost-effectiveness of prescribing and reduce medical costs[44–45]. It is vital that in the near future physicians and other healthcare professionals are provided targeted, evidence-based information on biosimilars to support their uptake and to gain the full cost-saving potential of these medicines[46–47]. The educational efforts from medical societies is also vital in the distribution of appropriate biosimilar information[11].

Physicians' attitudes towards biosimilars and means to enhance the uptake

According to this study, physicians' attitudes towards biosimilars are contradictory and the prescribing of biosimilars is more often directed to biologic-naïve patients. This is despite of convincing evidence that supports switching[48]. Prescribing decisions can either be made by individual physicians or, if thereafter necessary, they can be steered by binding policies that vary across countries. Furthermore, besides actual steering policies, there are general differences across health systems in prescribing, dispensing, pricing and reimbursement of biologic medicines that may effect on the uptake. [10-11]. For example in Denmark and Norway, hospital, regional or national tendering is in use, resulting in significant savings in the purchase of biologic medicines[11, 49–50]. Some countries have implemented incentives for healthcare professionals[11]. Prescription quotas that define the ratio of biosimilars of all prescribed biologic medicines, are in use in Germany and Sweden[51], while gain-sharing agreements that enable using the savings from biosimilar uptake to be used in the benefit of the clinic or the organisation are used in Sweden and in the United Kingdom[52–53]. Pharmacist-led substitution of biologic medicines can also be seen as a potential mean to enhance the uptake of biosimilars[11, 31]. Pharmacist-led substitution is legislatively possible in France and in the United States, and for some biological medicines in Australia[54–56]. Furthermore, the implementation of pharmacist-led substitution is currently ongoing in some European countries[46,57]. All these initiatives highlight that the weak uptake of biosimilars has been acknowledged globally, and there is a need to discover sustainable means to enhance and stabilize their uptake[11]. What complicates the issue is that, for example in Europe, even though the biosimilarity between biologic medicines is stated by the European Medicines Agency, the decisions on the interchangeability and substitution are made at the national level. In order to support the uptake of biosimilars, educational measures for both healthcare professionals and patients are needed, although the role of national recommendations, policies and steering for switching and substitution of biologic medicines should not be understated[31,46–47].

Strengths and limitations

Main strengths of our review are that the literature search was conducted with the help of an experienced information specialist, and that the step-by-step review and inclusion of publications as well as the quality evaluation of studies was conducted independently by two researchers in order to avoid bias[58]. Compared to the previous systematic review[12], altogether twelve original publications were added due to a wider literature seach focus. Furthermore, in the current study conference papers and Letters to Editors were excluded as for the purpose of the quality assessment, full information about the methodology of the included studies was needed. One major limitation of this review was that the study-by-study data extraction was only done by one researcher. Furthermore, theses or reports by authorities that could have included research results were excluded from this study. In addition, any of the available protocols for quality assessment did not cover different types of study settings and the protocol used in this study was compiled from four separate protocols. In addition, included studies were conducted in different countries with unique regulatory laws and policies that undoubtedly effect on the uptake and prescribing of biosimilars in the national level. Regardless, it is vital to compile studies from different countries with different systems and policies in order to form a comprehensive view on the current situation on the uptake of biosimilars. One notable point is also that the data in the studies that were included in this review were mainly collected in 2017 or before. The topic is very timely and perceptions towards the uptake of biosimilars may change according to new research information, interventions and experience in using these medicines. Thus, there is a need to continue examining perceptions of physicians, both in general and with different disciplines, particularly with qualitative research methods. Further studies are needed to explore the differences between disciplines in the attitudes towards and prescribing of biosimilars as the reasons behind these differences were not possible to explore in detail based on the studies included in this review.

Practical implications

This systematic review provides up-to-date knowledge on the physicians' perceptions on the uptake of biosimilars and highlights the need for further education and steering upon this issue. The knowledge provided by the review may be utilised in visioning future means to enhance the uptake of biosimilars that could include information sharing and educational interventions by means of e.g. academic detailing. Uptake of biosimilars may also be enhanced by implementing national policies or steering procedures to support the uptake, by means of pharmacist-led substitution of biologic medicines, for example.

5 CONCLUSIONS

This systematic review concludes that physicians' knowledge on and attitudes towards biosimilars vary. Although physicians have positive attitudes towards biosimilars, prescribing is limited, especially for patients that are already treated with biologic medicines. Perceptions towards the pharmacist-led substitution of biologic medicines are often negative. Education and national recommendations and policies for switching and substitution of biologic medicines are needed to support the uptake of biosimilars.

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COMPETING INTERESTS

Authors declare no competing interests.

AUTHOR'S CONTRIBUTIONS

KS, MM, JJ and KHA contributed to the conception or study design. KS and MM acted as principal investigators in the search and evaluation of the literature and in the quality assessment. KS drafted the manuscript. All authors participated in critical revision of the manuscript and approved the final version.

PATIENT CONSENT

Not required.

ETHICAL CONSENT

Not required.

PATIENT AND PUBLIC INVOLVEMENT

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

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FIGURE LEGENDS

Figure 1. PRISMA flow chart explaining the study inclusion process.

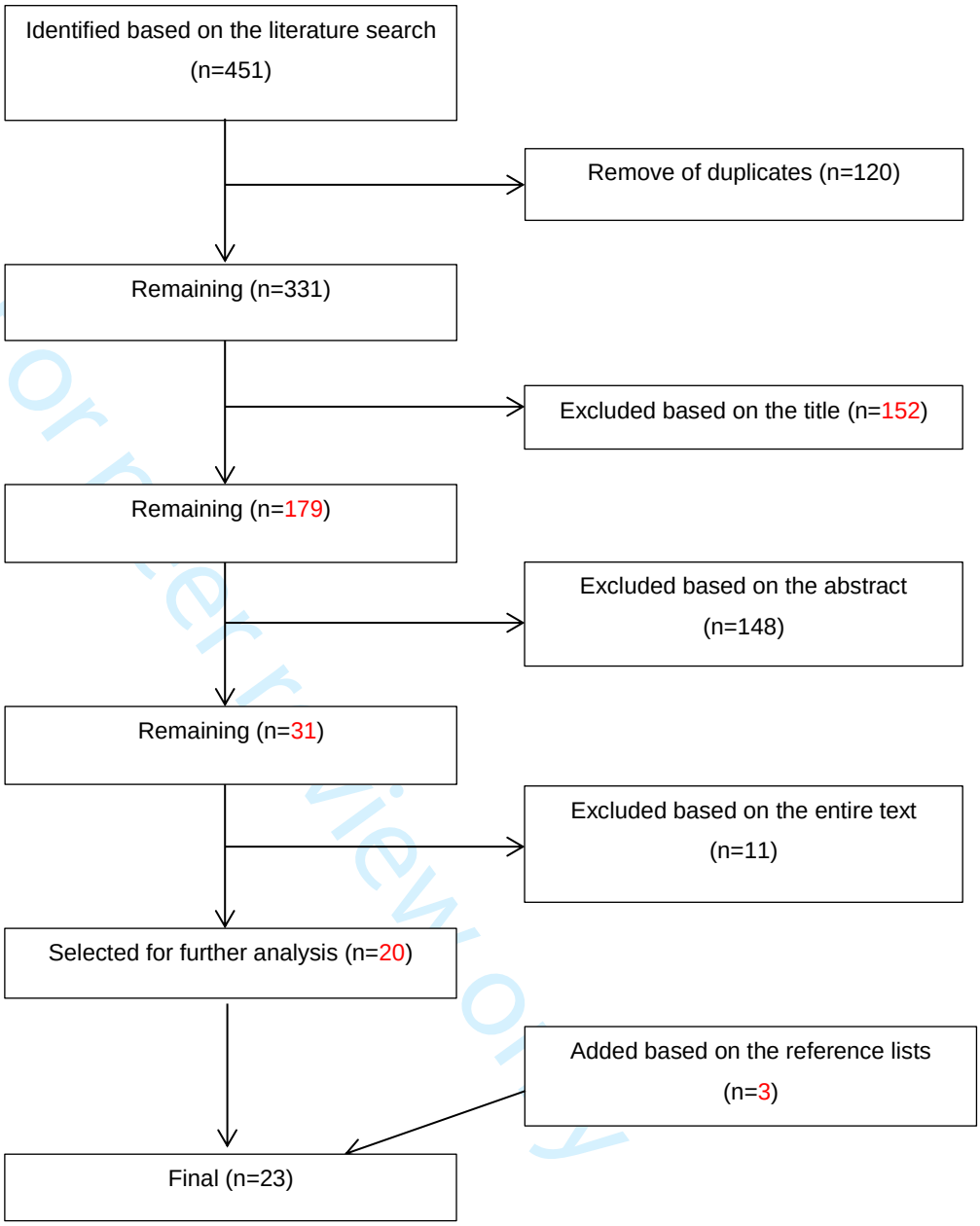

Figure 1. Flow chart on the review process.

Appendix 1. Literature search approach.

Database	Search terms
MedLine Ovid	(attitude* or stance* or opinion* or position* or orientat* or insight* or esteem* or estimat* or percepti* or belie* or decision* or decide* or determin* or prescrib* or chose* or choos* or choice* or guid* or recommend* or commission* or adopt* or accept* or uptak* best practice).mp AND (((physician.mp. or Physicians/) OR (clinician* or doctor* or specialist* or consultant*).mp.) AND (exp dermatology/ or exp internal medicine/ or exp endocrinology/ or exp gastroenterology/ or exp rheumatology/)) OR (exp general practice/ or exp family practice/ or exp general practitioners/ or exp hospitalists/ or exp physicians, family/ or exp physicians, primary care/or physician.mp. or Physicians/ or (clinician* or doctor* or specialist* or consultant*).mp.) AND (exp DIABETES MELLITUS/ or diabetes.mp.)) AND (exp Biosimilar Pharmaceuticals/ or biosimilar*.mp.) (attitude* or stance* or opinion* or position* or orientat* or insight* or esteem* or estimat* or percepti* or belie* or decision* or decide* or determin* or prescrib* or chose* or choos* or choice* or guid* or recommend* or commission* or adopt* or accept* or uptak* best practice).mp AND (((Physicians/ or (physician* or clinician* or doctor* or specialist* or consultant*).mp.) AND (exp Biosimilar Pharmaceuticals/ or biosimilar*.mp.)
Scopus	TITLE-ABS-KEY (biosimilar* AND (((physician* OR clinician* OR doctor* OR specialist* OR consultant*) W/20 (rheumatology OR gastroenterology OR endocrinology OR dermatology OR diabetes OR "internal medicine")) OR (rheumatologist* OR gastroenterologist* OR endocrinologist* OR dermatologist* OR hospitalist OR "General Practitioner*" OR physicians W/2 family)) AND (attitude* OR stance* OR opinion* OR position* OR orientat* OR insight* OR esteem* OR estimat* OR percepti* OR belie* OR decision* OR decide* OR determin* OR prescrib* OR choice* OR choos* OR chose* OR "best practice" OR guidi* OR guide* OR recommend* OR commission* OR adopt* OR accept* OR uptak*)) AND (LIMIT-TO (SRCTYPE , "j ") OR LIMIT-TO (SRCTYPE , "p ")) AND (LIMIT-TO (DOCTYPE , "ar ") OR LIMIT-TO (DOCTYPE , "re ") OR LIMIT-TO (DOCTYPE , "cp ") OR LIMIT-TO (DOCTYPE , "ip ")) AND (LIMIT-TO (LANGUAGE , "English ")) TITLE-ABS-KEY(biosimilar* AND (physician* OR clinician* OR doctor* OR specialist* OR consultant*) AND (attitude* OR stance* OR opinion* OR position* OR orientat* OR insight* OR esteem* OR estimat* OR percepti* OR belie* OR decision* OR decide* OR determin* OR prescrib* OR choice* OR choos* OR chose* OR "best practice" OR guidi* OR guide* OR recommend* OR commission* OR adopt* OR accept* OR uptak*)) AND (LIMIT-TO (SRCTYPE,"j ") OR LIMIT-TO (SRCTYPE,"p ")) AND (LIMIT-TO (DOCTYPE,"ar ") OR LIMIT-TO (DOCTYPE,"re ") OR LIMIT-TO (DOCTYPE,"cp ") OR LIMIT-TO (DOCTYPE,"ip ")) AND (LIMIT-TO (LANGUAGE,"English "))

Appendix 2. Quality assessment protocol.

Date:

Evaluator:

Authors:

Title:

Design	**Yes**
Meta-analysis	
Randomized controlled trial	
Systematic review	
Quantitative study: type (survey, pilot, other)	
Qualitative study: type (interview, focus group, other)	
Other, what?	

	Yes (1p)	**Partly (½p)**	**No (0p)**	**Notes**
Aim and context				
1 Is there an explicit aim?				
2 Is the context described?				
Methodology				
3 Is the data collection described accurately and is it repeatable?				
4 Is the sample selection preventative/relevant/not strategic (sample selected intentionally)?				
5 Is the dropout described?				
6 Is the data analysis described accurately and is it repeatable?				
7 Are the (statistical or other) methods adequate and applicable in relation to the aims of the study?				
Results				
8 Are the findings logic, reliable and clearly displayed?				
Discussion and conclusions				
9 Is there a critical discussion on the findings?				
10 Is there a critical discussion on the method?				
11 Is there a new value?				
12 Are the aims of the study met in the results and findings of the study?				
13 Are the instruments valid?				
14 Are the instruments reliable?				
Ethics				
15 Is there an ethical discussion?				
16 Are the authors non-dependable and free of any conflicts of interest?				
17 Did the participants participate without receiving a fee?				
TOTAL POINTS				

Quality assessment (rounded upwards when necessary): high: ≥ 15 yes, moderate: 12-14.5 yes, low: < 12 yes

Quality assessment protocol adapted from the protocols of Åkesson et al. (2006), Tong et al. (2007), Joanna Briggs Institute (2014) and Swedish Agency for Health Technology Assessment and Assessment of Social Services (2016).

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on section (in the main document without
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page, p1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Title page, p1, according to BMJ Open abstract structure
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, starting from p2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Objectives (at the last paragraph of the Introduction), p2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Material and methods, paragraph: Quality assessment, with an appendix and appropriate referencing, p3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Tables 1 and 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Appendix 1 in the Supplementary Files
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1 in the Supplementary Files
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Material and methods: Literature search, p2–3 and Table 1, p3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Material and methods: Data extraction and analysis, p3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Material and methods: Data extraction and analysis, p3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Material and methods: Quality assessment, p3 and Table 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on section
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results: Quality assessment, Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, p14 onwards, Tables 2 and 3
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, p14 onwards
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusions, p14 onwards
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding, p15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Physicians' perceptions of the uptake of biosimilars - A systematic review

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Physicians' perceptions of the uptake of biosimilars - A systematic review

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ABSTRACT

Objectives: To examine physicians' perceptions of the uptake of biosimilars

Design: Systematic review

Data Sources: MedLine Ovid and Scopus databases at the end of 2018.

Eligibility Criteria: Original scientific studies written in English that addressed physicians' perceptions of the uptake of biosimilars.

Data extraction and synthesis: The search resulted in altogether 451 studies and 331 after removing duplicates. Two researchers examined these based on the title, abstract and entire text, resulting in twenty studies. The references in these 20 studies were screened and three further studies were included. The data of these 23 studies were extracted. All the publications were quality assessed by two researchers.

Results: Most of the selected studies were conducted in Europe, and commonly utilized short surveys. Physicians' familiarity with biosimilars varied: 49–76% were familiar with biosimilars while 2–25% did not know what biosimilars were, the percentages varying from study to study. Their measured knowledge was generally more limited compared to their self-assessed knowledge. Physicians' perceptions of biosimilars also varied: 54–94% were confident prescribing biosimilars, while 65–67% had concerns regarding these medicines. Physicians seemed to prefer originator products to biosimilars, and prescribed biosimilars mainly for biologic-naïve patients. They considered cost savings and the lower price compared with the originator biologic medicine as the main advantages of biosimilars, while their doubts were often related to safety, efficacy and immunogenicity. 64–95% of physicians had negative perceptions of pharmacist-led substitution of biologic medicines.

Conclusions: Physicians' knowledge of and attitudes towards biosimilars vary. Although physicians had positive attitudes towards biosimilars, prescribing was limited, especially for patients already being treated with biologic medicines. Perceptions of pharmacist-led substitution of biologic medicines were often negative. Education and national recommendations for switching and substitution of biologic medicines are needed to support the uptake of biosimilars.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first systematic review conducted solely on physicians' perceptions regarding the uptake of biosimilars.
- The literature search was conducted with the help of an experienced information specialist.
- Publications selected for this review were quality evaluated by two researchers independently.
- The quality evaluation protocol was compiled from four existing evaluation protocols.
- The data in the studies included in this review were mainly collected before 2017.

KEYWORDS

biosimilar, biologic medicine, physician, perception, systematic review

1 INTRODUCTION

Biologic medicines consist of one or multiple biologic active substances and are often manufactured through biotechnology[1-2]. They were first developed mainly for rare diseases, but have also improved the treatment of many common diseases such as diabetes, arthritis and psoriasis[1]. The flipside of this transformation are the high costs of biologic medicines, which have contributed to increased medical costs globally[3].

Biosimilars are biologic medicines highly similar to the originator biologic medicines and with the same standards of quality, safety and efficacy[2-4]. Biosimilars are not clinically meaningfully different from the existing reference product. They are not regarded as generic medicines due to the complex manufacturing process and the natural variability between manufacturing batches of biologic medicines. The comparability of the product with the reference product has to be demonstrated, but clinical trials are not required. As a result, biosimilars can be brought to the market at a lower cost in comparison with the originator biologic product. The uptake of biosimilars could lead to healthcare cost savings and better patient access to costly biologic therapies[5]. By the end of 2018, 50 biosimilars had received marketing authorisation in Europe and 15 in the United States[6-7].

Despite their demonstrated comparability and cost-saving potential, biosimilars have not fully penetrated the market of biologic medicines. The European Union accounts for 80% of the global biosimilar market, but biosimilars constitute only 1% of the total sales of biologic medicines[8-9]. It has been stated that decisions to select biologic medicines may be either policy driven or made by individual physicians, which has raised the need to assess the prescribing of biosimilars in a critical manner[10-11]. Physicians' reluctance to prescribe biosimilars may restrict potential savings in medical costs that could enable biologic treatment of larger patient populations and provide more cost-effective treatment, as similar benefits could be gained by using less expensive treatments. Therefore, it is vital to study physicians' attitudes towards and perceptions of the uptake of biosimilars. The published information on the topic is somewhat contradictory. A previous systematic review focused on health care providers' knowledge, perceptions and prescribing behaviors of biosimilar medicines[12]. As the role of physicians is critical in the uptake of biosimilars and gaining the cost-saving potential, a wider understanding of physicians' perceptions of the uptake of biosimilars with a critical quality evaluation of the published literature was needed. Thus, the aim of this systematic review was to examine physicians' perceptions of the uptake of biosimilars.

2 MATERIAL AND METHODS

Literature search

A systematic literature search was conducted in the MedLine Ovid and Scopus databases at the end of 2018. These databases provide a comprehensive selection of scientific publications from the disciplines of pharmacy and medicine. The systematic search strategy (**Appendix 1**) was constructed by the research group, and the search was conducted by an experienced information specialist.

The initial search resulted in 451 studies. After removal of duplicates (n = 120), 331 studies remained. These studies were examined based on the title, abstract and entire text by two researchers independently (KS and MM). Of the 331 studies, 152 were excluded based on the title, 148 based on the abstract and 11 based on the entire text. At each stage, the researchers shared their views of the studies, discussed possible differences of opinion

and reached a consensus opinion based on the discussion. The inclusion and exclusion criteria of this systematic review are presented in **Table 1**. A total of 20 publications were selected for further analysis. Furthermore, the reference lists of these 20 articles were screened and three further articles that met the inclusion criteria were selected and included in this review, bringing the final number of included studies to 23. The PRISMA flow chart explaining the study inclusion process is presented in **Figure 1**.

Table 1. Inclusion and exclusion criteria of studies of this systematic review.

Inclusion criteria	Exclusion criteria
• Original primary studies	• Other than original primary studies, such as reviews, conference papers, consensus papers, commentaries and letters to editors
• English language	• Other language than English
• Investigating physicians' perceptions on the uptake of biosimilars (physicians in particular or at least 45% of physicians among other healthcare professionals, although only physicians perceptions were taken into account in this review)	• Investigating other healthcare professionals' perceptions on the uptake of biosimilars or publications with less than 45% of physicians of all participants involved or in which the physicians' perceptions are not separated in the results of the study
• Publications on the physicians' perceptions on the automatic substitution of biologic medicines	• Publications on the physicians' perceptions on the automatic or generic substitution of other medicines than biologics

Quality assessment

Each of the 23 selected studies was concisely reviewed. Quality assessment was conducted according to a protocol adapted from the protocols of Åkesson et al. (2006), Tong et al. (2007), the Joanna Briggs Institute (2014) and the Swedish Agency for Health Technology Assessment and Assessment of Social Services (2016)[13–16] (**Appendix 2**). The adapted protocol was developed and used in the quality evaluation because the study designs of the included studies varied and there was no single protocol that was suitable for evaluating the studies in a concise manner. Two researchers conducted quality assessments individually and then compared their reviews. Differences in opinions (n = 6) were discussed and final evaluation was reached by consensus. In the Results section of this systematic review, the studies assessed as having high quality are emphasized more than those with moderate or low assessed quality.

Data extraction and analysis

A meta-analysis was not conducted due to the various methods and inclusion of both qualitative and quantitative approaches in the studies included in this review. The following information was extracted from the included studies: general information (authors, year of publication, and country of publication), aims, methods and results. In regard to results, seven topics for data extraction were identified based on the topics discussed in the publications and discussions within the research group. These topics concerned the physicians' 1) self-rated knowledge of biosimilars, 2) measured knowledge of biosimilars, 3) information sources about biologic medicines, 4) attitudes towards and experienced advantages and disadvantages of biosimilars, 5) actions in the initiation of biosimilars for biologic-naïve patients, 6) actions in switching between originators and biosimilars for patients already being treated with biologic medicines, and 7) thoughts on pharmacist-led substitution of biologic medicines. In the Results section of this systematic review, these seven topics are presented within four broader themes: physicians' 1) self-rated and measured knowledge of biosimilars and information sources on biologic medicines, 2) attitudes towards and experienced advantages and disadvantages of biosimilars, 3) perceptions of the treatment initiations with biosimilars and on the switches between originator biologic medicines and biosimilars, and 4) attitudes towards

pharmacist-led substitution of biologic medicines. All percentages presented in this article refer to the percentages shown in the included studies of physicians with a certain opinion If more than one study investigated the topic, the ranges of percentages in these studies are shown.

3 RESULTS

Study characteristics

Physicians' perceptions of biosimilars have been studied mainly in Europe (n = 16)[10, 17–30] and North America (n = 4)[31–34]. Single studies have been conducted in Australia (n = 1)[35], New Zealand (n = 1)[36], Central and South America (n =1)[37] and with participants from multiple African, European and Middle Eastern countries (n = 1)[38] (**Table 2**). All the studies were published between 2014 and 2019, most of them (n = 20)[10, 17,20–22,24–34,35–38] in 2017 or earlier. The data presented in the studies were collected between 2013 and 2017. Most of the 23 selected publications utilized surveys, typically web-based questionnaires with 11–22 questions, or fully structured short interviews (n = 17)[10, 17–18,22–27,30–32,34,35–38]. In addition there were one qualitative interview study[19] and two real-world cross-sectional studies (n = 2)[28–29], in which physicians filled a survey form and reported their prescribing, then recruited patients who also filled a questionnaire form to provide information on how the reported prescribing was actualized in practice. There were also discrete choice method surveys (n = 2)[20–21], in which prescribers were given a hypothetical scenario and possible treatment options, and had to choose their preferred alternative[39]. Furthermore, there was one literature review with a survey of the market uptake of biosimilars[33].

5

Table 2. Characteristics of the 23 studies included in this systematic review.

Reference (Country or region)	Aims and methods	Results						
		Self-rated knowledge	Measured knowledge	Information sources	Attitudes towards and experienced advantages and disadvantages of biosimilars	Initiation of biosimilars (biologic-naïve patients)	Switches between originators and biosimilars (patients already treated with biologicals)	Pharmacist-led substitution of biologic medicines
Akhmetov et al. 2015[17] (Ukraine)	Endocrinologists', oncologists', nephrologists', immunologists' and rheumatologists' awareness of biosimilars Short interviews with eight close-ended questions, including 6 Likert-type items (n = 82), time of the study not reported	Low to medium levels (not reported more specifically) of biosimilar awareness on a 1-5 scale, where 1=low and 5=high) Endocrinologists and nephrologists had higher levels of awareness than other respondents	N/A	Peer-reviewed journal articles (n = 35), internet (n = 31), medical conferences (n = 20), popular press (n = 9), key-opinion leaders (n = 3), drug manufacturers (n = 2)	On a 1-5 scale, likelihood of prescribing biosimilars: 68% average (specific numbers not reported), 23% below average and 9% above average Majority (n not reported) are likely to try biosimilars in small batches, and then gradually move to larger groups of patients, endocrinologists and nephrologists showing the greatest interest Facilitators of prescribing: 39% cost advantage, 22% certification of safety by EMA or FDA, 22% certification of efficacy by EMA or FDA, 10% propitiousness of the Cabinet of Ministers and 7% trust towards European, American and Japanese biotech companies as importers Majority (n not reported) required 40-50% lower price for biosimilars than original biologics, endocrinologists typically accepting 20-30% discount in comparison to rheumatologists and oncologists that anticipated over 50% discount	N/A	N/A	N/A
Aladul et al. 2019[18] (the United Kingdom)	Knowledge and attitudes of healthcare professionals (n = 150 dermatologists, diabetologists, gastroenterologists and rheumatologists) towards infliximab and insulin glargine biosimilars Web-based survey via selected medical associations between August 2016 and January 2017	80% were aware that biosimilars were available on their local formulary	76% correctly considered biosimilars as copies of originators	N/A	91% considered robust pharmacovigilance studies and 84% the costs as the most important influencer of their prescribing of biosimilars	22% had major concerns on the efficacy and 14% on the safety of biosimilars that prevented them of starting a biosimilar	50% had major concerns on the efficacy and 34% on the safety of biosimilars in the switches	N/A
Aladul et al. 2018[19] (the United Kingdom)	Perceptions of consultants with specialties of diabetes mellitus, ulcerative colitis, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis (n = 10) towards biosimilar infliximab, etanercept and insulin glargine and potential barriers and facilitators to their prescribing Semi-structured interviews of purposive convenience sample of West Midlands hospital staff between June-November 2017	N/A	All interviewees expressed an understanding of the concept of biosimilars and believed biosimilars were copies of originators	Conferences, pharmaceutical industry representatives, scientific journals and colleagues	Majority of rheumatologists and diabetologists (n not reported) would prescribe the reference product if the prices of the reference product and the biosimilar are equal Gastroenterologists expressed more confidence and fewer concerns than other specialists, stating that indication extrapolation had previously been the major obstacle in the biosimilar uptake, but that it had been overcome Majority of rheumatologists (n not reported) had concerns on indication extrapolation, considering their patients are very sensitive with higher multimorbid risks. Some rheumatologists (n not reported) openly declared being mistrustful on biosimilars Facilitators of prescribing were information from societies, authorities and national registries. Barriers of prescribing were unexpected adverse effects or increase in side effects, patients' reluctance on using biosimilars, complicated, unsuitable or non-user-friendly administration device, unavailability of dose strengths in comparison to originators	Majority (n not reported) were content to initiate biosimilars Minority of rheumatologists and diabetologists (n not reported) felt under pressure to initiate new patients with biosimilars by their organization Two rheumatologists were happier to initiate biosimilars rather than switching	All gastroenterologists (n = 7) and a minority of rheumatologists (n not reported) were content to switch patients from reference products to a biosimilar All those that were content with switching considered that patients should be given the choice between the products Majority of all physicians (n not reported) felt multiple switching based on cost reasons irrational	Majority (n not reported) has negative view on the pharmacist-led substitution of biologic medicines Minority (n not reported) considered that automatic substitution would be accepted in the next few years
Baji et al. 2016a[20] (Hungary)	Gastroenterologists' treatment preferences in ulcerative colitis Discrete choice experiment survey (in which prescribers are given hypothetical scenario and possible treatment options, and they are asked to choose the alternative they prefer[39]) in a Hungarian professional society meeting in 2014 (n = 51)	N/A	N/A	N/A	20% had no concerns on biosimilars, 67% had some concerns on efficacy and/or safety and 12% did not support the use of biosimilars due to the lack of RCT evidence	84% of all physicians and 80% of those who had some concerns (67%) chose biosimilar in at least one choice set The most important attribute driving the choice: stopping rule (whether treatment after 12 months is reimbursed) Estimated probability of choosing the originator over biosimilar in the present reimbursement situation: 48%. Probability of choosing the biosimilars with all the benefits offered over the originator in the present situation: 85% versus 15%	61% of all and 53% of those who were concerned chose biosimilar in at least one of the choice sets The most important attribute driving the choice: stopping rule Estimated probability of choosing the originator over biosimilar in the present reimbursement situation: 71%. Probability of choosing the biosimilars with all the benefits offered over the originator in the present situation: 63% versus 37%	N/A

Baji et al. 2016b[21] (Hungary)	Gastroenterologists' treatment preferences in Crohn's disease Discrete choice experiment survey (in which prescribers are given hypothetical scenario and possible treatment options, and they are asked to choose the alternative they prefer[39]) in a Hungarian professional society meeting in 2014 (n = 51)	N/A	N/A	N/A	20% had no concerns on biosimilars, 65% had some concerns on efficacy and/or safety and 12% did not support the use of biosimilars due to the lack of RCT evidence Four clinicians were classified to "No biosimilar" attitude group, 19 to the "Biosimilar to new patients only" group and 27 to the "Biosimilar" group (one clinician was excluded from the analysis)	Men, senior consultants, working in inflammatory bowel disease centre and treating more patients were more likely to consider biosimilars for biologic-naïve patients only Estimated probability of choosing the originator over biosimilar, when no benefits are offered for using the biosimilar: 60%. Probability of choosing the biosimilar with all kinds of benefits over the originator: 89% versus 11% The most important attribute driving the choice: continuity of medicine supply	Estimated probability of choosing the originator over biosimilar, when no benefits are offered for using the biosimilar: 74%. Probability of choosing the biosimilar with all kinds of benefits over the originator: 44% versus 56% The most important determinant of choice: type of the treatment	N/A
Barsell et al. 2017[31] (USA)	Dermatologists' knowledge and perceptions of biosimilars, whether a practice gap exists and to study misconception and barriers to biosimilar usage Web survey of 14 multiple-choice questions for the members of five state dermatologic societies and National Psoriasis Foundation in 2015 (n = 97)	62% responded having basic understanding of biosimilars, 27% complete understanding and 11% that they have never heard of biosimilars	37% were aware that biosimilars are highly similar to the reference product, 26% described biosimilar as "generic", 27% described them as same bio-drug with equal bioequivalence and 10% said they did not know the definition. Those with complete understanding (27%), 21% incorrectly described biosimilar as "generic"	35% self-study, 25% scientific publications, 17% conferences and seminars, 3% biosimilar company-sponsored events and 20% other	Advantages: 71% low price to patients, 68% easier access to treatment and 65% low price to payers. Disadvantages: 71% efficacy, 66% potential switch to biosimilar without physicians' knowledge, 66% safety and 63% immunogenicity. 8% believed there were no advantages Convincing physicians of interchangeability: 44% extensive phase I, II and III studies, 37% valid longitudinal data from patient registries, 37% same level of testing (not specified more thoroughly) than generic medicines, 36% evidence of pharmacokinetic and pharmacodynamic equivalence	25% definitely or highly likely to prescribe a biosimilar 38% will try it on very selected patients	N/A	88% believed that pharmacist-led substitution without consulting physicians will be allowed in the future 76% very important and 18% somewhat important to have control over whether patients receive originator or biosimilar
Beck et al. 2016[22] (France)	Knowledge, experience and opinions related to biosimilars and to identify expectations, barriers and possible options to promote prescription Web survey of 22 questions for nearly 500 rheumatologists in 2015 (n = 116)	55%/3% considered they had little/no knowledge of biosimilars 5% felt very well-informed Hospital-based rheumatologists were likely to be more familiar with biosimilars compared to office-based rheumatologists 98% had at least one question about biosimilars	85% thought biosimilars are similar to reference products that had gone off-patent; 85% considered biosimilars have no meaningful differences in quality, 80% in safety and 90% in efficacy; 65% thought that the assessment of biosimilarity requires more comprehensive data than generic drugs; and 46% believed that biosimilar marketing authorisation is granted on the sole investigation of pharmacokinetic bioequivalence	84% self-study and scientific publications, 76% pharmaceutical companies, 72% continuous training, 54% physician colleagues and 19% pharmacist colleagues	44% agree and 10% strongly agree being in favour of implementation of biosimilars Positive factors: 90% healthcare cost savings, 61% releasing of resources allowing treating additional patients, 49% positive impact on patients' access to innovative medicines and 46% health policy-makers incentives. Barriers: 67% indication extrapolation of efficacy and safety, 66% lack of information about tolerability, 59% risk of increasing patients' concerns, 57% lack of clinical trials and 55% patients' wishes to be treated with the originator	7% had already prescribed biosimilars mentioned in the survey 89% considered it was conceivable to start a treatment for biologic-naïve patients	25% could envision a switch	58% strongly disagree and 23% disagree of approving substitution by a pharmacist
Chapman et al. 2018[23] (the United Kingdom)	Healthcare professionals' knowledge and attitudes towards infliximab and insulin glargine biosimilars and factors influencing their prescribing and compare healthcare professionals' attitudes with the utilisation of these biosimilars in hospitals Web-based survey of 11 questions for societies of dermatology, diabetology, gastroenterology and rheumatology in 2016-2017 and drug utilisation analysis from DEFINE database in 2015-2016 (n = 234). Other stakeholders apart from physicians are not addressed in this review	N/A	72% correctly thought biosimilars are similar copies of biologic medicines, 18% thought biosimilars are generic biologic medicines, 3% counterfeit medicines, 3% had heard of them but did not know what they were, 3% had never heard of them and 1% new biological medicines 75% knew biosimilars were available on their local formulary	N/A	Gastroenterologists were most frequent prescribers of biosimilars (prescribing every day or week), followed by rheumatologists, diabetologists and dermatologists The dominant consideration: cost saving Increasing the use of biosimilars: regulatory guidance and robust pharmacovigilance studies, local policy, potential cost saving to organisation (whether or not savings were invested in the prescribers' department) and robust cost-effectiveness data of biosimilar vs. originator	95% and 90% of gastroenterologists, 92% of rheumatologists, 79% of dermatologists and 75% of diabetologists had no or minor concerns on safety 90% of gastroenterologists, 88% of rheumatologists, 74% of dermatologists and 68% of diabetologists had no or minor concerns on efficacy	95% of gastroenterologists, 53% of rheumatologists, 78% of dermatologists and 69% of diabetologists had no or minor concerns on safety 93% of gastroenterologists, 55% of rheumatologists, 79% of dermatologists and 65% of diabetologists had no or minor concerns on efficacy	N/A
Cohen et al. 2016[32] (USA)	Dermatologists', gastroenterologists', haematologist-oncologists', medical oncologists', nephrologists' and rheumatologists' awareness, knowledge, and	N/A	92% of dermatologists, 90% of gastroenterologists, 83% of rheumatologists, 74%	88% scientific journals, 73% FDA and 64% physician peers. Trust to media was less than 5%	Generally positive attitudes towards biosimilars. Dermatologists and rheumatologists appear less enthusiastic	N/A	91% open to switching patients to a biosimilar	N/A

	perceptions of biosimilars over time (survey will be repeated in 2-3 years) Survey of 19 questions in 2015-2016 (n = 1201)		of nephrologists, 69% of haematologist-oncologists and 63% of medical oncologists were aware which of the listed medicines in their specialty were biologic 56% of rheumatologists, 33% of gastroenterologists, 31% of dermatologists, 15% of nephrologists, 9% of medical-oncologists and 3% of haematologist-oncologists incorrectly reported there are no biosimilars available		62% considered the biosimilar will have equivalent efficacy as its originator and 57% that the biosimilar will be at least as safe as the originator 58% had concerns on patient compliance and access to treatments options with originators Positive factors: increased access and utilization of biologic medicines, expanded treatment options and provided savings for the healthcare system			
Danese et al. 2016[24] (Europe, countries not reported)	Evolution on thinking about biosimilars one year after they had become available in the EU. Comparison to the survey published by Danese et al. 2014[24] Web survey with 14 multiple-choice questions for members of European Crohn's and Colitis Organization in 2015 (n = 118)	56% judged that educational activities that they were exposed to was fair and adequate, while 16% found it unnecessary	N/A	More information was hoped from 75% medical societies, 52% multispecialty safety registries, 47% health institutions and 26% guidelines	29% totally confident, 18% very confident and 34% confident enough (5%, 8% and 26% in 2013) to prescribe a biosimilar Main advantage: 92% (90% in 2013) cost-sparing. Main issue: 42% the lack of data from clinical trials for all indications 27% (67% in 2013) consider biosimilars have higher immunogenicity compared to the originator and 17% (43% in 2013) different action than the originator 51% (24% in 2013) thought biosimilar should be approved for all the indications of the originator	N/A	44% (6% in 2013) would switch a patient with remission	89% (85% in 2013) disagreed with automatic substitution by a pharmacist 13% support substitution for new prescriptions and 13% for all patients
Danese et al. 2014[25] (Europe, countries not reported)	Awareness of and readiness to use biosimilars Web survey of 15 questions for 1,000 randomly selected European Crohn's and Colitis Organization members in 2013 (n = 307)	N/A	70% were aware that biosimilar is a similar copy, but not equal to the originator, 19% responded that it is a copy of biological agent, identical to the originator, like a generic	Preferred information: 81% multi-specialty international safety registries to monitor safety and effectiveness, 78% health institutions on the development of rules on the use of biosimilars, 66% medical societies, 61% data regarding the registration process for biosimilars and 57% multispecialty practice guidelines	6% thought that the originator and biosimilar were interchangeable The main advantage: cost-sparing (89%). The main issue: different immunogenicity pattern than the originator (67%) 50% agreed biosimilars can significantly reduce healthcare costs, 27% expected them only having a marginal impact, 6% expected additional costs of introduction, regulation and pharmacovigilance to offset any potential savings 24% agreed that the tested biosimilar could be approved for all indications of the originator in terms of safety and efficacy, 19% for all rheumatologic indications, 14% for the specific indication only, 3% stated that all biosimilars could be approved for all indications of the originator and 39% disagreed with all of the above	61% felt little or no confident in using biosimilars in their everyday clinical practice, 26% confident enough, 8% very confident, and 5% totally confident	28% would consider replacing originator with a biosimilar	64% against the substitution by pharmacist 18% would agree only for new patients
Farhat et al. 2016[38] (Algeria, Belgium, Egypt, Iran, Iraq, Italy, Jordan, Lebanon, Sudan and Syria)	Parameters on the acceptance and future prescription of biosimilars and worldwide situation focusing mainly on the EU and US laws, regulations and legislative pathways, pricing and challenging market access Survey for over 150 healthcare professional in the conference meeting in 2015 (n = 117 health care professionals responded, of which most were physicians; exact number of physicians who responded not reported). Other stakeholders apart from physicians are not addressed in this review	N/A	66% knew what biosimilars were, 12% did not know and 22% had not answered the question. Of those who knew (66%), 62% considered biosimilars bioequivalent to originator and have all preclinical and clinical trials equal to the originator 63% agreed that biosimilars are already marketed in the Arab and Middle Eastern markets, while 45% agreed that they are manufactured in the same region	N/A	Drivers for prescribing: 69% FDA or EMA approval, 65% lower price of bioequivalence in comparison to the originator, 48% bio-efficacy, 42% safety and 31% good manufacturing practices and high reputation of the manufacturer. 5% think biosimilars don't have advantages 35% considered the cost of treatment should not overcome its effectiveness or safety/tolerance 26% thought lower prices were good news as patients will be treated with biologics 27% consider biosimilars would bring cost savings 49% trust companies highly experienced in manufacturing small-molecule generic drugs and 55% companies with prior experience in manufacturing biologics as biosimilar producers	41% prescribe biosimilars while 33% don't (note that respondents were also other than physicians)	N/A	N/A
Felix et al. 2014[33] (USA)	Challenges and opportunities of market uptake of biosimilars from the perspectives of physicians and payers Survey for physicians that had written about or were familiar with biosimilars based on literature	N/A	N/A	N/A	Almost all physicians (n not reported) believed that if biosimilar was approved by FDA it will perform similarly to the originator with regard to safety and efficacy Influences of decision making: efficacy and safety, out-of-pocket costs to the patient, price of treatment and immunogenicity	Four physicians are somewhat likely, six very likely and three not likely to prescribe a biosimilar to a new patient	31%/61% (n not reported) say they are somewhat likely/very likely to switch an existing patient from originator to biosimilar	N/A

	review of Medline-indexed publications (n = 14). Other stakeholders apart from physicians are not addressed in this review				50% (n not reported) consider it is very important that there are proven chemical and pharmacokinetic similarities between originators and biosimilars Roughly half (n not reported) consider payer and cost considerations very important			
Gewanter & Reilly 2014[37] (Argentina, Brazil, Colombia and Mexico)	Understanding of biosimilars, how they use them and their concerns for the future Web-based survey for 6650 prescribers from global market research panel (n = 399)	35% did not consider themselves familiar with biosimilars, meaning they could not define them or had never heard of them	49% were aware of differences between biologicals, biosimilars and non-comparable biologicals. 30% were unaware that clinical trials for single indication lead to approval for multiple indications	71% seminars and conferences, 55% self-study, 32% education from biosimilar companies, 18% clinical trial participation and 4% other means 37% would like to learn from pharmaceutical companies	88% prescribe biologicals	50% said they believed if two biological medicines had the same non-proprietary scientific name, patient could receive either product and have the same result	44% said they believed if two biological medicines had the same non-proprietary scientific name, patient could be safely switched during a course of treatment, and the patient would have the same result 64% would not be comfortable switching for cost reasons rather medical reasons	N/A
Grabowski et al. 2015[34] (Canada)	Gaps in knowledge and attitudes towards biosimilars of rheumatologists Web-based survey of 29 questions for 369 members of Canadian Rheumatology Association in February 2014 (n = 81)	31% indicated themselves being familiar or very familiar with biosimilars Those with greater than 20 years of practice were significantly more likely to indicate themselves familiar or very familiar than those with 20 or less years of practice	66% considered biosimilars essentially same as generic drugs 38% were aware of Health Canada's guidance on clinical requirement for biosimilar approval	N/A	94% generally comfortable prescribing biologic medicines to their patients 31% comfortable prescribing biosimilars to their patients if biosimilar was currently available 29% declined until their colleagues recommend it 42% indicated a 30% price reduction, and a third a ≥50% price reduction being reasonable before payers mandated the use of biosimilars over brand name biologics 54% disagreed or strongly disagreed, 32% agreed or strongly agreed and 14% were neutral using biosimilars with extrapolated indications 49% not confident, 19% confident or very confident, and a third neutral on the long-term sustainability profile of the biosimilar with 30 weeks of head-to-head clinical trial	59% consider offering biosimilars, if biosimilar demonstrates that it is comparable to the brand name drug 72% unlikely or very unlikely, 11% likely or very likely and 16% neutral to offer a biosimilar, when biologic-naïve patient is an ideal candidate, where cost is not an issue Greater familiarity with established brand name drugs and uncertainty over the long-term safety of biosimilars were often cited among those unlikely or very unlikely offering biosimilars 54% did not typically prescribe a biosimilar, were likely or very likely to offer a biosimilar, when the provincial payer or insurance company mandated using a biosimilar	7.5% consider switching, if biosimilar demonstrates that it is comparable to the brand name drug	88% concerned or very concerned if a pharmacist had the ability to substitute a biologic drug for a biosimilar without the physician's approval
Hallersten et al. 2016[30] (France, Germany, Italy, Poland, Spain, Sweden, UK)	Preferences on type and detail of biosimilar information in Summaries of Product Characteristics (SmPC) and the use of information sources when prescribing biologics including biosimilars by dermatologists, endocrinologists, gastroenterologists, haematologists, nephrologists, oncologists and rheumatologists Web-survey with approx.. 30 multiple-choise questions for 210 physicians (30 from each of the country) who were members of panels of physicians (approximately 250-800 physicians per country) who agreed earlier to participate in such survey studies, in 2015	N/A	N/A	Frequently used information sources: 63% professional guidelines, 55% SmPCs, 51% peer reviewed journals, 42% national or hospital formularies The physicians preferred modified SmPC (modified for the purpose of the study) where additional information in the biosimilar label had been added, specifically: 1) clarifying which product (the biosimilar or the reference product) generated which clinical data, 2) inclusion of additional statements indicating that the product is a biosimilar, and 3) that similarity has been evaluated in preclinical and clinical studies.	N/A	N/A	N/A	N/A
Hemmington et al. 2017[36] (New Zealand)	Perceptions and attitudes towards efficacy, safety and manufacturing of biosimilars, factors associated with positive attitudes, indication extrapolation and switching, and circumstances in which physicians would be reluctant to prescribe biosimilars	76% reported being familiar and having basic understanding and 13% very familiar and complete understanding of biosimilars, 9% had heard of biosimilars,	N/A	N/A	70% very or somewhat confident of the efficacy of biosimilars Less than 20% had negative views Situations when biosimilars were not prescribed: 32% lack of clinical data, 17% evidence of adverse effects or lack of efficacy, 15% patients do well with current treatment and 6% patients have complex medical history	71% would prescribe biosimilars for all or some clinical conditions meeting the relevant criteria, 10% would do this for only few or no clinical situations	51% confident and 28% not very confident or not at all confident to switch patients	N/A

	E-mail survey for 327 physicians in medical specialist society (n = 110)	but could not define them, and 2% had never heard of biosimilars			47% very confident or somewhat confident, 32% not confident and the remainder undecided in indication extrapolation			
O'Callaghan et al. 2017[10] (Ireland)	Medical specialists', general practitioners' and community pharmacists awareness of and attitudes to biosimilars E-mail-survey of 14-20 questions for 2917 physicians in national professional societies in 2016 (n = 253 analysed answers from general practitioners and n = 102 from medical specialists). Other stakeholders apart from physicians are not addressed in this review	44% of medical specialists and 5% of general practitioners very familiar with biosimilars, 41% and 35% familiar , and 6% and 25% had never heard the term "biosimilar"	25% of medical specialists and 18% of general practitioners considered biosimilars the same as generic medicines 31% of medical specialists incorrectly agreed that biological medicines sharing the same international non-proprietary name were "structurally identical"	Medical specialists (n = 101, not all answered this question): 72% guidelines from professional societies, 68% published literature and 63% educational events GPs (n = 247, not all answered this question): 58% national or hospital formularies	59% of those aware of biosimilars in their therapeutic area (n = 73) prescribed biosimilars, while 40% didn't Concerns: 81% efficacy in extrapolated indications, 81% immunogenicity, 79% efficacy, 78% safety, 73% quality and 62% traceability	67% of medical specialists that prescribed biosimilars (n = 43) would most likely prescribe a biosimilar for treatment initiation	28% of medical specialists that prescribed biosimilars (n = 43) would be likely to switch from originator to biosimilar	<5% of medical specialists would consider pharmacist-led substitution appropriate 49% consider decisions should be taken by the prescriber on treatment initiation and 61% during treatment course. 43% consider decisions should be agreed with clinician in advance on treatment initiation and 35% during treatment course 84% think notifications for physician very important or critical in treatment initiation and 90% during treatment course
O'Dolinar & Reilly 2014[26] (France, Germany, Italy, Spain and the United Kingdom)	Nephrologists', rheumatologists', dermatologists', neurologists', endocrinologists' and oncologists' attitudes on biosimilar naming, substitution, and knowledge, sources of information and need for further education on biosimilars Web-based 15-minutes short survey for 4,324 global physician market research panel of at the last quarter of 2013. 470 prescribers (20% of each five countries) completed the survey	46% responded having basic understanding, 43% complete understanding, 11% could not define biosimilars and 1% had never heard of biosimilars 53% incorrectly thought biosimilar and originator were structurally identical and 37% incorrectly believed biosimilars are clinically tested for all indications	N/A	47% conferences and seminars, 35% self-study, 11% studies sponsored by biosimilar companies and 6% equally studies sponsored by innovator companies, clinical trial participation and other routes	48% said it was very important, 24% critically important, 23% somewhat important, 4% slightly important and 1% not important to have a sole authority to select the medicine	47% considered that products with the same non-proprietary name could be safely given to a patient with same results, 40% didn't think that way	45% think patients can't be switched between the products with same non-proprietary names, 39% believed patients could be switched safely and effectively	62% not acceptable, 35% acceptable and 3% totally acceptable on pharmacist-led substitution 47% very important, 30% critical, 6% slightly important and 1% not important to receive a notification if the pharmacist had dispensed other than prescribed biologic medicine during a repeated treatment
van Overbeeke et al. 2017[27] (Belgium)	Knowledge and perceptions of patients and physicians with regard to originators and biosimilars and differences in perceptions and the factors influencing their preferences Web survey of multiple-choice and open-ended questions for all 232 Belgian rheumatologists in 2016 (n = 41 responded). Other stakeholders apart from physicians are not addressed in this review	95% considered biosimilars are similar, but not identical	90% were able to share the most complete definition of a biosimilar	N/A	7% had prescribed biosimilars. 73% preferred the originator when the prices were equal and 38% when originator was more expensive. When prices were equal, none preferred biosimilar. 93% considered price, 63% safety, 61% quality and 61% efficacy as sources of differences between originators and biosimilars 33% considered biosimilars and originators interchangeable if biosimilarity is proven in the same indication and 38% in indications where the medicine works via the same biological mechanism. 28% considered that biosimilars and originators were never interchangeable 56% think extrapolation could only be performed if efficacy and safety is proven to be similar in one of the indications and if the medicine works via the same mechanism in the other indications. 39% stated the indications should never be extrapolated Positive influencers: clinical trials with positive results and clinical data in the respective indication. Negative influencers: less studied than the originator and no clinical trials in the respective indication	8% would not prescribe a biosimilar and 60% would only prescribe a biosimilar to biologic-naïve patients.	N/A	N/A
Reilly & Murby 2017[35] (Australia)	Opinions on the naming of biologicals and biosimilars, how the use of these medicines is recorded and their views on substitution of, familiarity with, knowledge of, attitudes to and beliefs in biosimilars Web-based survey for prescribers recruited from a global, commercial database of health care professional in 2016 (n = 451, of which 160 completed the survey)	21% considered themselves very familiar and having complete understanding of biosimilars, 73% basic understanding and 6% could not define them	50% thought biosimilars go through the same regulatory process as original biologics 70% knew biosimilars could be approved for all or for some indications of the originator	46% published literature, 28% colleagues, 27% information from Pharmaceutical Benefits Advisory Committee, 24% product information label, 19% information from Therapeutic Goods Administration, 18% sales presentative, 13% hospital formulary	N/A	16% would be comfortable prescribing a biosimilar that was approved for several indications based on clinical trials in only one indication, 11% would not feel comfortable and 73% had some concerns on this	N/A	54% very and 36% critically important to have sole authority to decide of which biological was dispensed Evidence required for pharmacist-led substitution: 53% clinical trial data of no safety of efficacy risks in switching, 53% clinical trial data of no safety of efficacy risks

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				43% never used published literature				after multiple switches, 27% in-market experience, 24% observational data and 6% no evidence would be sufficient
Sullivan et al. 2017[28] (Germany)	Motivators of prescribing biosimilars, preferences matching actual prescribing behaviour and patient acceptance, satisfaction and concerns on biosimilars and how these relate to the treatment with originators or biosimilars Real world, cross-sectional study (in which physicians filled a survey form and reported their prescribing, and recruited patients that also filled a questionnaire form to provide information on how reported prescribing was occurred in practice) in 2015-2016 (n = 25). Other stakeholders apart from physicians are not addressed in this review Based on their response, 11 physicians were assigned to investigative (primarily concerned with symptom improvement and disease modification), 7 to conservative (primarily concerned with safety) and 7 to other (influenced primarily by other factors)	N/A	N/A	N/A	Biosimilars account for 12-13% of all biologic therapies the respondents prescribe Reasons to prescribe: desire to get experience with the new product (89% of investigative, 100% of conservative and 57% of other), being convinced of equivalent efficacy compared to originators (44%, 67% and 43%), lower cost (44%, 83% and 71%), believing that is economic prescribing (44%, 83% and 57%) and believing that using biosimilars makes savings which can be used elsewhere (22%, 67% and 29%)	88% would prefer to prescribe originator to biosimilar as 1st line therapy	N/A	N/A
Waller et al. 2017[29] (Germany)	Motivators of prescribing biosimilars, preferences matching actual prescribing behaviour, and patient acceptance, satisfaction and concerns on biosimilars and how these relate to the treatment with originators or biosimilars Real world, cross-sectional study (in which physicians filled a survey form and reported their prescribing, and recruited patients that also filled a questionnaire form to provide information on how reported prescribing was occurred in practice) in 2015-2016 (n = 50). Other stakeholders apart from physicians are not addressed in this review Based on their response, 23 physicians were assigned to investigative (primarily concerned with symptom improvement and disease modification), 17 to conservative (primarily concerned with safety) and 10 to other (influenced primarily by other factors)	N/A	N/A	N/A	Biosimilars constitute less than 10% of the biologic therapies the respondents prescribed Reasons to prescribe: desire to get experience with the new product (86% of investigative, 65% of conservative and 50% of other), being convinced of equivalent efficacy compared to originators (64%, 65% and 50%) and lower costs (64%, 71% and 88%)	>95% would prefer to prescribe originator to biosimilar as 1st line therapy	N/A	N/A

Quality assessment

Of the 23 included studies, seven[10,18,20–21,23,27,34] were evaluated as high, six[19,22,28–31] as moderate and nine[17, 24-26,32–33,35,37–38] as low in quality based on the criteria used in this review (**Table 3**). Publications evaluated as high in quality often included well-described and logically presented methods and results sections together with a critical discussion section, which those evaluated as moderate or low quality typically lacked. In general, the quality assessment revealed that there is a lack of valid instruments and studies utilizing qualitative research methods.

Self-rated and measured knowledge on biosimilars and sources of information (n = 18)

There was wide variation in physicians' self-rated knowledge of biosimilars (**Table 2**). Most physicians reported having at least a basic understanding of the topic: 5–44% reported that they were very familiar and 49–76% that they were familiar with biosimilars[10,24,26–27,31,34,35–36]. However, 2–25% of the physicians reported that they did not know what biosimilars are. Physicians with more years of practice and those with specialisation consider themselves more familiar with biosimilars in comparison to less experienced colleagues and general practitioners[10, 22,34].

Although according to their self-rating the physicians generally were familiar with biosimilars, their actual measured knowledge of the topic appeared to be weaker (**Table 2**). From 18% to 66% of the physicians incorrectly described biosimilars as generic medicines, whereas 31–72% thought they are structurally identical to originator medicines[10, 22–23,25,32,34–35,37–38]. However, in three studies, 76–100% were able to state the complete definition of a biosimilar correctly[18–19,27].

The physicians used several sources of information about biologic medicines, such as scientific publications (25–84%), self-study (35–84%), pharmaceutical companies (32–76%), guidelines from professional societies (26–75%), educational events and conferences (17–71%), other published literature (46–68%), physician colleagues (28–54%), safety registries (52%), and pharmacist colleagues (19%)[10,17,19,22,24–26,30–32,35,37] (**Table 2**). One study found that information sources may vary according to the physicians' educational background, as the most common information source for medical specialists were the guidelines from professional societies, whereas for general practitioners they were national or hospital formularies[10].

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Table 3. Summary of the quality evaluation of the 23 included studies of this systematic review.

Reference	Main strengths	Main limitations	Quality according to the quality assessment protocol
Aladul et al. 2019[18]	Results logically and clearly displayed	Details of the questionnaire form were not available, discussion on methodology partly lacking	High
Baji et al. 2016a[20]	Well-described and logically presented methodology, results and discussion	Ethical discussion lacking	High
Baji et al. 2016b[21]	Well-described and logically presented methodology, results and discussion	Critical and ethical discussion partly lacking	High
Chapman et al. 2018[23]	Mainly well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
Grabowski et al. 2015[34]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High*
Hemmington et al. 2017[36]	Well-described and logically presented methodology, results and discussion	Details of the questionnaire form were not available, more in-depth information could have been collected by a qualitative study	High
O'Callaghan et al. 2017[10]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
van Overbeeke et al. 2017[27]	Well-described and logically presented methodology, results and discussion	More in-depth information could have been collected by a qualitative study	High
Aladul et al. 2018[19]	Semi-structured interviews provide a more in-depth view on the perceptions of healthcare professional in comparison to short surveys	Exact numbers of respondents which certain opinion (n) not always reported, low number of representatives per each professional group	Moderate*
Barsell et al. 2017[31]	Well-presented results and discussion	Details of the questionnaire form were not available, description of methodology lacking, e.g. dropout not described, ethical discussion lacking	Moderate
Beck et al. 2016[22]	Well-presented results and discussion	Details of the questionnaire form were not available, validity of the instrument unclear, as more in-depth information could have been collected by a qualitative study, dropout not described accurately	Moderate*
Hallersten et al. 2016[30]	Results clearly presented	Details of the panel of physicians in different European countries where the respondents were reqruited were not shown. Critical discussion on the method partly lacking.	Moderate
Sullivan et al. 2017[28]	Results clearly presented	Dropout not described accurately, some inconsistencies in the presentation of methodology and discussion	Moderate*
Waller et al. 2017[29]	Well-presented results and discussion	Some inconsistencies in the presentation of methodology, e.g. sample selection and dropout	Moderate*
Akhmetov et al. 2015[17]	Explicit aims	Clear presentation of results lacking, critical and ethical discussion lacking	Low
Cohen et al. 2016[32]	Mainly well-presented results and discussion	Details of the questionnaire form were not available, description of methodology lacking, ethical discussion lacking	Low
Danese et al. 2016[24]	Results clearly presented	Details of the questionnaire form were not available, critical and ethical discussion partly lacking, description of methodology partly lacking	Low
Danese et al. 2014[25]	Results clearly presented	Statistical analyses lacking, critical and ethical discussion lacking, description of methodology partly lacking, for example the number of invited members not mentioned	Low
Farhat et al. 2016[38]	Mainly logically presented methodology	Aim is not explicitly presented, number of physicians who responded not reported, results presented in table format only, critical discussion lacking	Low*
Felix et al. 2014[33]	Explicit aims	Strategic sample selection, details of the questionnaire form were not available, exact numbers of respondents which certain opinion (n) not always reported, description of used statistical methods and data analysis lacking, inconsistency in the description of results	Low
Gewanter & Reilly 2014[37]	Explicit aims	Respondents from market research panel resulting that respondents work in disciplines in which don't necessarily involve biosimilars, such as psychiatry, description of used statistical methods and data analysis lacking, critical and ethical discussion lacking	Low
O'Dolinar & Reilly 2014[26]	Explicit aims	Intentional sample selection, clear presentation of results lacking, critical and ethical discussion lacking	Low
Reilly & Murby 2017[35]	Explicit aims	Description of data collection partly lacking, description of used statistical methods and data analysis lacking	Low

* Differences in opinions of which quality grade each publication was given, set in consensus

Attitudes towards and experienced advantages and disadvantages of biosimilars (n = 21)

The physicians' reported attitudes towards biosimilars seem contradictory[10, 20–25,27–29,31–34,36–38] (**Table 2**). Some (6–38%) physicians consider biosimilars and originator products interchangeable, while others (28%) never think so[25, 27]. Some studies show that 65–67% of physicians have concerns regarding biosimilars[20–21], while others report that 54–94% of physicians feel somewhat or very confident prescribing biosimilars[10, 22,24,34,36]. Regardless, a positive attitude towards biosimilars does not automatically translate into prescribing, as physicians seem to prefer originator products to biosimilars[20,27,34]. Some studies indicate that there might be differences in attitudes towards biosimilars between specialties: gastroenterologists seem to be frequent prescribers of biosimilars, while dermatologists and rheumatologists seem less enthusiastic[19,23,32].

The main experienced advantages of biosimilars are cost savings[18,22–25,31], lower price in comparison to the originator biologic medicine[31,38] and the possibility to get experience with the new product[28–29](**Table 2**). Additionally, single studies reported that robust pharmacovigilance studies[18], easier access to treatment for patients[31], and approval of the European Medicines Agency or the Food and Drug Administration[38] were motivators for prescribing biosimilars. The most commonly reported disadvantages were distrust in safety[10,18,22,31,33], efficacy[10,18,22,31,33], immunogenicity[10,25,31] and indication extrapolation of biosimilars[10,34] or the lack of clinical data on biosimilars[24,26]. Single studies also suggested that the quality[10], traceability[10] or tolerability[22] of biosimilars and patients' concerns towards biosimilars[22] were disadvantages.

Initiation of biosimilars and switches between original biologic medicines and biosimilars (n = 21)

The physicians (39–89%) seemed more willing to prescribe a biosimilar for biologic-naïve patients rather than for patients already being treated with biologic medicines[10,20,23,25,27–29,31,33–38] (**Table 2**). In discrete choice experiment studies, for example, 61–84% of gastroenterologists chose biosimilars in at least one of the choice sets for biological-naïve patients[20–21]. However, there are also other factors affecting the medicine selection, such as the cost of the medicines. One article reported that if cost were not an issue, only 11% of physicians would choose a biosimilar for treatment initiation[34]. Additionally, some studies suggest that some personal characteristics may influence the uptake of biosimilars by individual physicians: men, senior consultants and those treating more patients[21], along with those more familiar with brand name medicines and uncertain of the long-term safety of biosimilars[34] were often unlikely to choose a biosimilar as initial therapy. Within medical specialties, gastroenterologists (95% with no concerns) appear to be the most confident to use biosimilars in treatment initiations, followed by rheumatologists (92%), dermatologists (79%) and diabetologists (75%)[23].

The physicians did not seem willing to switch from an originator biologic medicine to a biosimilar[10,20–25,32–34,36–37] (**Table 2**). The proportion of physicians willing to switch from an originator to a biosimilar was 51 % or less, except in a single study in which the percentage was 91%[10, 22,24–25,32,34,36]. Similarly, when it comes to treatment initiation, the medical specialty of the physicians affected their willingness to switch biologic medicines[23]. Gastroenterologists (95% with no concerns) seemed the most confident concerning switching, followed by dermatologists (78%), diabetologists (69%) and, notably, rheumatologists (53%).

Pharmacist-led substitution of biologic medicines (n = 9)

Most physicians (64–95%) were concerned about or disagreed with pharmacist-led substitution of biologic medicines[10, 19,22,24–26,31,34–35] (**Table 2**). The studies suggest that having full autonomy in medicine selection and being fully aware of which medicines their patients receive was often crucial for physicians[10,26,31,35]. However, according to a single study, 88% of the physicians believed that pharmacist-led substitution without consulting physicians will be allowed in the future[31].

4 DISCUSSION

In this systematic review, physicians' knowledge of biosimilars varied widely. In general, their measured knowledge was weaker than their self-assessed knowledge. They used multiple sources of information about biologic medicines, most commonly scientific publications, pharmaceutical companies and professional societies. Similarly, their perceptions of biosimilars and the uptake of these medicines also varied. They seemed to prefer originator products to biosimilars, and prescribe biosimilars mainly for biologic-naïve patients. They consider cost savings and the lower price compared with the originator biologic medicines to be the main advantages of biosimilars, while their doubts wererelated to the safety, efficacy and immunogenicity of biosimilars. Most of the physicians had negative perceptions of pharmacist-led substitution of biologic medicines. The results in this review are in line with an earlier systematic review of healthcare providers' perceptions of biosimilars[12].

Physicians' knowledge of biosimilars

This study found that physicians' knowledge of biosimilars in many cases was inadequate, and this may contribute to the low prescribing and uptake of biosimilars[10,12,32]. Although this issue has been widely recognised, there is limited evidence of the effectiveness of education interventions on prescribing[40]. In contrast, academic detailing has proven to be effective in steering prescribing[41–42]. This is a method in which a trained educator meets with a healthcare professional and shares the latest evidence-based information on the topic concerned[43]. Besides its effectiveness in steering prescribing patterns, academic detailing has been proven to improve the cost-effectiveness of prescribing and reduce medical costs[44–45]. It is vital that in the near future physicians and other healthcare professionals are provided targeted, evidence-based information on biosimilars to support their uptake and to gain the full cost-saving potential of these medicines[46–47]. The educational activities of medical societies is also vital in the distribution of appropriate biosimilar information[11].

Physicians' attitudes towards biosimilars and means to enhance the uptake

According to this study, physicians' attitudes towards biosimilars were contradictory, and the prescribing of biosimilars is more often directed to biologic-naïve patients despite the convincing evidence that supports switching[48]. Prescribing decisions can either be made by individual physicians orsteered by binding policies that vary across countries. Furthermore, besides actual steering policies, there are general differences across health systems in prescribing, dispensing, pricing and reimbursement of biologic medicines that may have effects on the uptake.[10-11] In Denmark and Norway, for example, hospital, regional or national tendering is in use, resulting in significant savings in the purchase of biologic medicines[11, 49–50]. Some countries have implemented incentives for healthcare professionals[11]. Prescription quotas defining the ratio of biosimilars of all prescribed biologic medicines are in use in Germany and Sweden[51], while profit-sharing agreements making it possible to use the savings from biosimilar uptake for the benefit of the clinic or the organisation are used in Sweden and the United Kingdom[52–53]. Pharmacist-led substitution of biologic medicines can also be seen as a potential means to enhance the uptake of biosimilars[11, 31]. This is legislatively possible in France and in the United States, and for some biological medicines also in Australia[54–56]. Furthermore, the implementation of pharmacist-led substitution is currently ongoing in some European countries[46,57]. All these initiatives highlight that the weak uptake of biosimilars has been acknowledged globally, and there is a need to discover sustainable means to enhance and stabilize their uptake[11]. What complicates the issue is that, for example in Europe, even though the biosimilarity between biologic medicines is stated by the European Medicines Agency, decisions on the interchangeability and substitution are made at the national level. In order to support the uptake of biosimilars, educational measures for both healthcare professionals and patients are needed, although the role of national recommendations, policies and steering in the switching and substitution of biologic medicines should not be understated[31,46–47].

Strengths and limitations

The main strengths of our review are that the literature search was conducted with the help of an experienced information specialist, and that the step-by-step review and inclusion of publications as well as the quality evaluation of studies was conducted independently by two researchers in order to avoid bias[58]. Compared to the previous systematic review[12], this review included twelve more original publications due to a wider literature seach focus. Furthermore, the current study excluded conference papers and Letters to Editors because for the purpose of the quality assessment full information about the methodology of the included studies was needed. One major limitation of this review is that the study-by-study data extraction was done by only one researcher. Furthermore, theses or reports by authorities that could have included research results were excluded from this study. In addition, none of the available protocols for quality assessment covered different types of study settings, so the protocol used in this study was compiled from four separate protocols. Moreover, the included studies were conducted in different countries with unique regulatory laws and policies that undoubtedly affect the uptake and prescribing of biosimilars at the national level. However, it is vital to compile studies from different countries with different systems and policies in order to form a comprehensive view of the current situation concerning the uptake of biosimilars. Another notable point is that the data in the studies included in this review were mainly collected in 2017 or earlier. The topic is very timely and perceptions of the uptake of biosimilars may change in light of new research information, interventions and experience in using these medicines. Thus, there is a need to continue examining physicians' perceptions, both in general and with different disciplines, particularly with qualitative research methods. Further studies are needed to explore the differences between disciplines in the attitudes towards and prescribing of biosimilars, as the reasons behind these differences could not be explored in detail based on the studies included in this review.

Practical implications

This systematic review provides up-to-date knowledge about physicians' perceptions of the uptake of biosimilars, and highlights the need for further education and steering on this issue. The knowledge provided by the review may be utilised in visioning future means to enhance the uptake of biosimilars that could include information sharing and educational interventions by means of, e.g., academic detailing. The uptake of biosimilars may also be enhanced by implementing national policies or steering procedures that support the uptake, by means of pharmacist-led substitution of biologic medicines, for example.

5 CONCLUSIONS

This systematic review shows that physicians' knowledge of and attitudes towards biosimilars vary. Although physicians have positive attitudes towards biosimilars, prescribing is limited, especially for patients already being treated with biologic medicines. Perceptions of the pharmacist-led substitution of biologic medicines are often negative. Education and national recommendations and policies for switching and substitution of biologic medicines are needed to support the uptake of biosimilars.

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COMPETING INTERESTS

Authors declare no competing interests.

AUTHOR'S CONTRIBUTIONS

KS, MM, JJ and KHA contributed to the conception or study design. KS and MM acted as principal investigators in the search and evaluation of the literature and in the quality assessment. KS drafted the manuscript. All authors participated in critical revision of the manuscript and approved the final version.

PATIENT CONSENT

Not required.

ETHICAL CONSENT

Not required.

PATIENT AND PUBLIC INVOLVEMENT

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

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FIGURE LEGENDS

Figure 1. PRISMA flow chart explaining the study inclusion process.

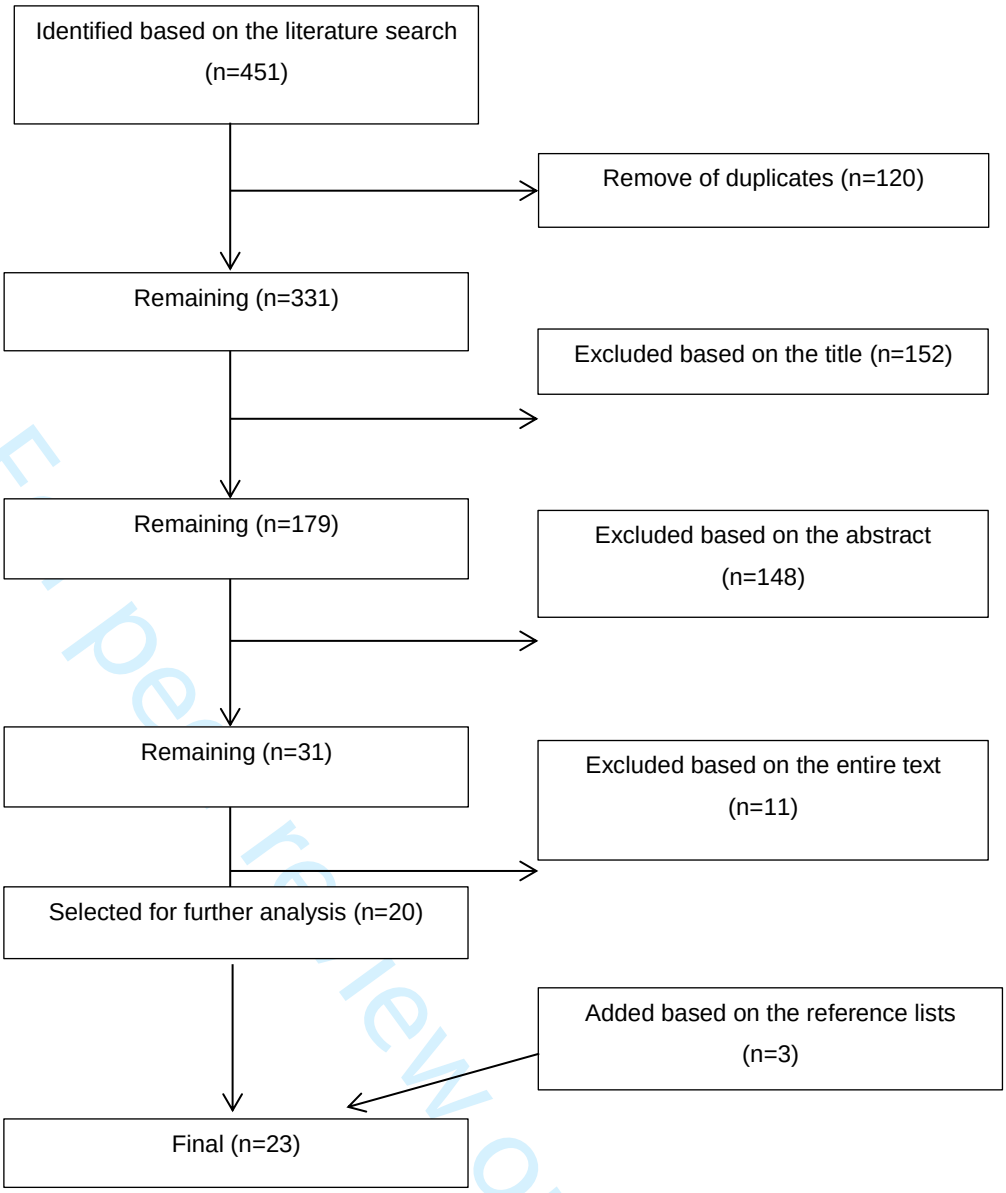

Figure 1. Flow chart on the review process.

Appendix 1. Literature search approach.

Database	Search terms
MedLine Ovid	(attitude* or stance* or opinion* or position* or orientat* or insight* or esteem* or estimat* or percepti* or belie* or decision* or decide* or determin* or prescrib* or chose* or choos* or choice* or guid* or recommend* or commission* or adopt* or accept* or uptak* best practice).mp AND (((physician.mp. or Physicians/) OR (clinician* or doctor* or specialist* or consultant*).mp.) AND (exp dermatology/ or exp internal medicine/ or exp endocrinology/ or exp gastroenterology/ or exp rheumatology/)) OR (exp general practice/ or exp family practice/ or exp general practitioners/ or exp hospitalists/ or exp physicians, family/ or exp physicians, primary care/or physician.mp. or Physicians/ or (clinician* or doctor* or specialist* or consultant*).mp.) AND (exp DIABETES MELLITUS/ or diabetes.mp.)) AND (exp Biosimilar Pharmaceuticals/ or biosimilar*.mp.) (attitude* or stance* or opinion* or position* or orientat* or insight* or esteem* or estimat* or percepti* or belie* or decision* or decide* or determin* or prescrib* or chose* or choos* or choice* or guid* or recommend* or commission* or adopt* or accept* or uptak* best practice).mp AND (((Physicians/ or (physician* or clinician* or doctor* or specialist* or consultant*).mp.) AND (exp Biosimilar Pharmaceuticals/ or biosimilar*.mp.)
Scopus	TITLE-ABS-KEY (biosimilar* AND (((physician* OR clinician* OR doctor* OR specialist* OR consultant*) W/20 (rheumatology OR gastroenterology OR endocrinology OR dermatology OR diabetes OR "internal medicine")) OR (rheumatologist* OR gastroenterologist* OR endocrinologist* OR dermatologist* OR hospitalist OR "General Practitioner*" OR physicians W/2 family)) AND (attitude* OR stance* OR opinion* OR position* OR orientat* OR insight* OR esteem* OR estimat* OR percepti* OR belie* OR decision* OR decide* OR determin* OR prescrib* OR choice* OR choos* OR chose* OR "best practice" OR guidi* OR guide* OR recommend* OR commission* OR adopt* OR accept* OR uptak*)) AND (LIMIT-TO (SRCTYPE , "j ") OR LIMIT-TO (SRCTYPE , "p ")) AND (LIMIT-TO (DOCTYPE , "ar ") OR LIMIT-TO (DOCTYPE , "re ") OR LIMIT-TO (DOCTYPE , "cp ") OR LIMIT-TO (DOCTYPE , "ip ")) AND (LIMIT-TO (LANGUAGE , "English ")) TITLE-ABS-KEY(biosimilar* AND (physician* OR clinician* OR doctor* OR specialist* OR consultant*) AND (attitude* OR stance* OR opinion* OR position* OR orientat* OR insight* OR esteem* OR estimat* OR percepti* OR belie* OR decision* OR decide* OR determin* OR prescrib* OR choice* OR choos* OR chose* OR "best practice" OR guidi* OR guide* OR recommend* OR commission* OR adopt* OR accept* OR uptak*)) AND (LIMIT-TO (SRCTYPE,"j ") OR LIMIT-TO (SRCTYPE,"p ")) AND (LIMIT-TO (DOCTYPE,"ar ") OR LIMIT-TO (DOCTYPE,"re ") OR LIMIT-TO (DOCTYPE,"cp ") OR LIMIT-TO (DOCTYPE,"ip ")) AND (LIMIT-TO (LANGUAGE,"English "))

Appendix 2. Quality assessment protocol.

Date:

Evaluator:

Authors:

Title:

Design	**Yes**
Meta-analysis	
Randomized controlled trial	
Systematic review	
Quantitative study: type (survey, pilot, other)	
Qualitative study: type (interview, focus group, other)	
Other, what?	

	Yes (1p)	**Partly (½p)**	**No (0p)**	**Notes**
Aim and context				
1 Is there an explicit aim?				
2 Is the context described?				
Methodology				
3 Is the data collection described accurately and is it repeatable?				
4 Is the sample selection preventative/relevant/not strategic (sample selected intentionally)?				
5 Is the dropout described?				
6 Is the data analysis described accurately and is it repeatable?				
7 Are the (statistical or other) methods adequate and applicable in relation to the aims of the study?				
Results				
8 Are the findings logic, reliable and clearly displayed?				
Discussion and conclusions				
9 Is there a critical discussion on the findings?				
10 Is there a critical discussion on the method?				
11 Is there a new value?				
12 Are the aims of the study met in the results and findings of the study?				
13 Are the instruments valid?				
14 Are the instruments reliable?				
Ethics				
15 Is there an ethical discussion?				
16 Are the authors non-dependable and free of any conflicts of interest?				
17 Did the participants participate without receiving a fee?				
TOTAL POINTS				

Quality assessment (rounded upwards when necessary): high: ≥ 15 yes, moderate: 12-14.5 yes, low: < 12 yes

Quality assessment protocol adapted from the protocols of Åkesson et al. (2006), Tong et al. (2007), Joanna Briggs Institute (2014) and Swedish Agency for Health Technology Assessment and Assessment of Social Services (2016).

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on section (in the main document without
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page, p1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Title page, p1, according to BMJ Open abstract structure
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, starting from p2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Objectives (at the last paragraph of the Introduction), p2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Material and methods, paragraph: Quality assessment, with an appendix and appropriate referencing, p3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Tables 1 and 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Appendix 1 in the Supplementary Files
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1 in the Supplementary Files
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Material and methods: Literature search, p2–3 and Table 1, p3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Material and methods: Data extraction and analysis, p3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Material and methods: Data extraction and analysis, p3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Material and methods: Quality assessment, p3 and Table 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on section
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results: Quality assessment, Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, p14 onwards, Tables 2 and 3
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, p14 onwards
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusions, p14 onwards
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding, p15

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