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SYSTEMATIC REVIEW

Is There Any Research Evidence Beyond Surveys and Opinion Polls on Automatic Substitution of Biological Medicines? A Systematic Review

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Abstract

Background Biosimilars are expected to decrease growing health care expenditures. Given that uptake of biosimilars has been modest, automatic substitution has been suggested to increase their use, but the practice is not yet allowed or implemented in many jurisdictions.

Methods A systematic review was performed by searching databases Scopus, Medline (Ovid), CINAHL, and Web of Science. Peer-reviewed, original studies written in English and published during the period January 1, 2006 to April 24, 2021 reporting any interventions, pilots or any other studies including experiences or perceptions of any relevant stakeholders on automatic substitution of biologics were included without limitation by setting or geography. The quality of the included studies were evaluated by pre-determined criteria.

Results Altogether, 27 studies fulfilled the inclusion criteria, of which 23 were surveys, and four semi-structured interviews reporting mainly stakeholders' perceptions on automatic substitution. Most of the studies (56%, 15/27) were from Europe. Studies were conducted among prescribers ($n = 12$), pharmacists ($n = 5$), patients ($n = 4$), payers ($n = 1$), and mixed stakeholders ($n = 5$). The primary objective of the majority (81%, 22/27) of the studies was to investigate some other biosimilar topic than automatic substitution. The reported perceptions of substitution were mainly negative. Studies evaluating risks, safety or effectiveness, or reporting real-life experiences of biologic substitution were lacking except one intervention and two prospective risk management studies. The overall quality of the studies was low to moderate, and the results were not generalizable due to convenience sampling not representing the populations of interest, and low response rates.

Conclusions The current research evidence on the automatic substitution of biologics is scarce and of low to moderate quality, reflecting low stakeholder knowledge and their cautious attitude towards biosimilars. The safe and efficient implementation of automatic substitution requires well-designed practices, pilot studies, and evolving legislation.

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1 Introduction

Biological medical products (biologics) are essential for the treatment of many serious and chronic conditions such as diabetes, other autoimmune diseases, and cancer [1]. However, biologics are expensive drugs, adding to growing health care costs across Western societies [2, 3]. A biosimilar is a biological medicinal product highly similar to another biological medicinal product ('reference medicine') already marketed in the European Union (EU) [1, 4]. As forerunners in biosimilar use, the EU countries have had them in clinical use for more than a decade without any major safety concerns [1, 5]. Biosimilars are expected to trigger the desired price competition between biosimilars and their reference medicines, but only if effectively introduced [6, 7].

Key Points

Even though automatic substitution of biologics has been suggested to be a potential strategy for controlling growing healthcare costs, the identified evidence is mainly based on opinion polls and surveys of low to moderate quality, yielding results that are neither generalizable nor suitable for guiding policy making.

The negative perceptions of stakeholders, dominated by opinions of prescribing physicians, may be influenced by methodological limitations of the studies, limited knowledge and understanding about biologicals including biosimilars in general, and lack of real-life experience of the automatic substitution of biologics.

Future research should head toward systematic approaches and well-designed intervention and effectiveness studies to gain more robust evidence on the potential benefits and risks of procedures facilitating automatic substitution of biologics.

Efficient biosimilar uptake has been limited by the reluctance of prescribers to initiate a patient's medication with a biosimilar or to switch a reference medicine to a biosimilar, and their perceptions have been studied earlier in this respect [8, 9]. Stakeholders' hesitancy in using biosimilars may be increased by varying positions of regulatory agencies regarding interchangeability [10], that is, medicine's property to be exchanged with another medicine, which is expected to have the same clinical effects [1]. However, there are routine transitions between interchangeable medicines in EU hospitals, partly driven by tendering procedures [11].

Automatic substitution is a practice of dispensing one medicine instead of another interchangeable and equivalent medicine at the pharmacy without consulting the prescriber [1]. Automatic substitution is considered to be a potential strategy to increase biosimilar uptake. The substitution can occur by hospital pharmacists if the local legislation allows the dispensing of biologics to be covered by the hospital budget and if biosimilars are available as an option in the hospital drug formulary and practices [12–16]. The substitution of biologics has been considered more controversial in the outpatient setting. Only a few countries, among them some EU countries and Australia, allow limited automatic substitution of biologics in community pharmacies, for example to treatment naïve patients or with certain products [12, 17]. In the United States, a framework exists to permit automatic substitution (i.e., 'interchangeability'), but to date, no biosimilar has cleared the regulatory hurdle to gain interchangeable status [12, 18, 19], and even then the final decision to allow substitution remains with the individual state [20].

Despite a few substitution-pioneering countries, governments' overall enthusiasm to promote biologics substitution has been low. This may reflect an evolving biosimilar debate, as a few years ago the safety of a switch (physician-led transition) was still under active debate among policymakers [21]. Current debate on safety of multiple switches may soon shift to discussion on practical implementation of automatic biologic substitution. Therefore, we systematically summarized available research evidence on practices, experiences, and perceptions of any relevant stakeholders on automatic substitution of biological medicines.

2 Methods

This systematic review focused on peer-reviewed literature of interventions, pilot reports and any other studies including experiences and perceptions of the relevant stakeholders such as healthcare professionals and patients, concerning automatic substitution of biologics. The systematic review was conducted by following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [22].

2.1 Search Strategy

A systematic literature search was conducted on the databases Scopus, MEDLINE (Ovid), CINAHL, and Web of Science, which were considered to cover the relevant literature of interest. The combination of search terms focused on the terms 'substitution' and 'biosimilar'. Synonyms and kindred terms were identified to enable an extensive search since global biosimilar terminology is not established [23–25]. Two library information specialists assisted with the search terms independently, and the wider search strategy was chosen. In all four databases, the following search query was used: (substitution* OR switch* OR interchang*) AND (biosimilar* OR "similar biotherapeutic*" OR "subsequent entry biologic*" OR "SEB" OR biogeneric* OR "follow-on biologic*").

The search was performed in February 2020 and repeated on April 24, 2021 to cover the most recent literature. The peer-reviewed literature from January 1, 2006, to April 24, 2021, were included. This time frame was chosen to identify the recent literature, limiting the results to the time since the biosimilars were authorized for the first time [26]. The search was limited to articles in English. Also, the reference lists of identified articles and systematic reviews related to automatic substitution of biologics were hand-searched and screened for relevance.

2.2 Eligibility Criteria

A predetermined PICOS tool was applied to select the studies for inclusion [22]. Participants were defined as patients, healthcare professionals, or any other stakeholders related to the topic. Intervention was defined as pharmacist-led automatic substitution of biological medicinal products containing the same active ingredient. Comparison was not required, and any scientifically rigorous research method was allowed. The outcome under study was either any outcome of the intervention (substitution), or experiences, perceptions or opinions of patients, healthcare professionals, or other stakeholders about automatic (pharmacist-led) substitution of biologics. The setting was limited to community and hospital pharmacies providing that a prescriber was not involved in the transition.

An article was included in the systematic review if it met the following predetermined inclusion criteria: an original peer-reviewed study on intervention studies, pilots or experiences, perceptions or opinions of relevant stakeholders including healthcare professionals and patients of an automatic substitution of biologics. Studies reporting the legislative status or practice of substitution without any outcome measures (i.e., studies aiming to provide information on whether substitution was allowed but not how it was practiced) were excluded. Position papers, narrative reviews, letters, editorials, conference abstracts, and meeting reports were excluded. Prescriber-led switching studies, clinical trials on safety and/or efficacy of biosimilars, clinical trial extensions, and real-world data reports focusing on the safety and/or efficacy of biosimilars were excluded. Also, pre-clinical studies, molecular structure studies, and studies investigating the mechanism of action were outside the scope of this systematic review.

2.3 Study Selection and Data Extraction

The database search yielded 2880 citations (Fig. 1). Once duplicates were removed, 1363 potentially relevant citations were identified for further screening. Two authors (HMT and JF) independently screened titles and abstracts for relevance. Discrepancies were solved by discussion. The full texts of the remaining citations were reviewed, and those that fulfilled inclusion criteria were selected. The reference lists of identified articles and topic-related systematic reviews were hand-searched and screened for relevance. Finally, 27 articles were included in further analysis and quality assessment.

Relevant data were extracted from the included articles. Extraction items were chosen by three authors (HMT, JF, and MA) with consensus. When an article consisted of several study parts, only substitution-related parts were included in the analysis. The extracted information included authors of the article, publication year, journal, affiliation types of the authors, study aim, study description, how substitution-related issues were studied or asked, main outcomes, study limitations identified by authors, and funding sources with other relevant disclosures reported in the article. Included articles were primarily analyzed by one author (HMT), and the other authors reviewed the results.

2.4 Qualitative Analysis of Data

For data processing, the extracted information was classified according to the study type, continent, country, data collection period, the occupation or background of the participants, and their perceptions and experiences of automatic substitution of biologics. When the data collection period was not reported, it was set to the submission date of the article.

The identified perceptions and experiences of the study participants were categorized into three segments. The studies with more than half of the participants opposing automatic substitution of biologics were classified in the segment on negative perceptions. The studies where more than half of the participants favored automatic substitution were classified in the segment on positive perceptions. The studies where the participants' perceptions were uncertain or unclear were classified as uncertain. The legislative status of substitution of biologics in the country of the study was extracted from the literature, where available. No statistical analysis was performed.

2.5 Quality Assessment

As all the included studies applied survey and qualitative interview methodology, their quality was evaluated according to the Survey Assessment Guide [27] and the CASP Qualitative Studies checklist [28], respectively. These assessment protocols were chosen in order to capture method-specific quality features being aware that both instruments are not designed for scoring of the quality of studies.

Each survey (with or without intervention study design) was systematically evaluated by seven main questions (Electronic Supplementary Material [ESM] 1) [27]. Each main question had a maximum of eight sub-questions. The main questions were scored depending on the distribution of sub-questions that fulfilled the requirement. The main question was scored as '1' if more than 66% of the sub-questions were answered 'yes.' The main question was scored '0.5' if 33–65% of the sub-questions were answered 'yes,' and the rest were scored as '0.' The total quality of the included surveys was calculated based on the scores attained from the main questions, the maximum being 7 points. A survey with a total score of 4.5 (64% of the maximum score of 7) or higher was ranked as a high-quality survey. A survey

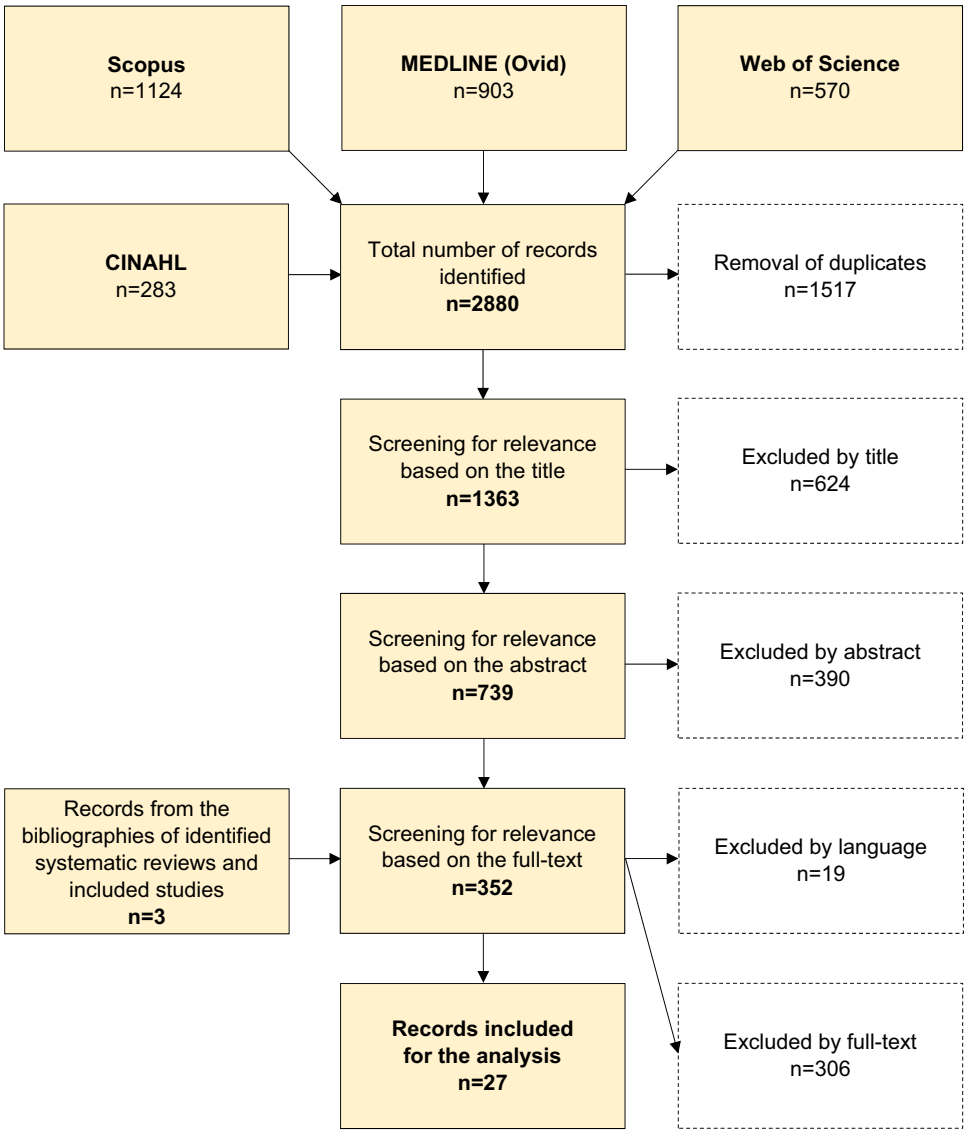

Fig. 1 Flow chart of study selection

with a total score of 2.5 (36% of the maximum score of 7) or lower was deemed a low-quality survey. All identified studies were included in the further analysis regardless of their methodological quality.

The quality of each semi-structured interview study was assessed through a 10-item critical appraisal checklist [28], to ensure that included qualitative interviews were of applicable quality (received more than 8/10 points from the checklist) (ESM 1). However, the quality of the qualitative interviews were not compared. One author (HMT) carried out the quality assessment. All the other authors carefully reviewed the assessment before the approval.

3 Results

3.1 Characteristics of Included Studies

The systematic search resulted in 27 original articles, of which 22 were non-interventional surveys and one had an intervention study design while the remaining four studies were semi-structured interviews (Table 1, Table 2, ESM 2). No study was designed as a comparative study or a study reporting practical or clinical treatment outcomes on biologics automatic substitution.

The majority (56%, 15/27) of the included studies were conducted in Europe [29–43], followed by North America ($n = 4$) [44–47], Australia ($n = 2$) [48, 49], Pakistan ($n = 1$) [50], Russia ($n = 1$) [51], Tunisia ($n = 1$) [52], Latin America ($n = 1$) [53], mixed in France and Canada ($n = 1$) [54], and mixed in Asian countries ($n = 1$) [55]. The study

participants were physicians ($n = 12$) [30, 36, 37, 39, 44, 45, 47, 48, 51–53, 55], pharmacists ($n = 5$) [31, 38, 43, 50, 54], patients ($n = 4$) [32, 34, 40, 49], payers ($n = 1$) [46], or various stakeholders ($n = 5$) [29, 33, 35, 41, 42]. All semi-structured interviews had participants of various stakeholders and were from Europe [29, 33, 35, 42]. In 44% of the studies (12/27), the data collection had begun in 2015 or earlier [29, 30, 36–41, 45–47, 53]. Almost one third of the studies (8/27) were conducted in countries that allowed limited pharmacist-led automatic substitution of biologics [32, 38, 39, 48, 49] or substitution was not specifically prohibited at the time of data collection [31, 33, 43]. Most of the studies (81%, 22/27) had a primary focus other than automatic substitution of biologics. Substitution or replacement of biologics was mentioned as an objective only in five studies [30, 33, 34, 43, 48], of which one was a qualitative study focusing on automatic substitution of biologics [33].

The authors of the majority (89%, 24/27) of the studies were affiliated with academia, a government authority, a hospital or university hospital, or a hospital pharmacy [29, 31–47, 49, 51, 52, 54, 55]. Three studies (11%) did not report any government-, academic-, or health system-affiliated authors [30, 48, 53]. The pharmaceutical industry was reported as one of the affiliations in three studies [41, 44, 51]. Studies that reported any funding were partly or fully funded by either a public sector, i.e., government authority, university grant or bursary (3/27) [33, 43, 47], research fund [35], pharmaceutical industry (5/27) [40, 44–46, 51], or a lobbying organization (3/27) [30, 48, 53]. One study [41] had received both public and pharmaceutical industry funding. In the rest of the included studies, authors declared no funding received for the study [29, 31, 34, 36–39, 42, 49, 50, 52, 55] or the funding was not reported in their article [32, 54]. However, potential conflicts of interest among authors were reported in 63% (17/27) of the studies [29, 30, 33, 35–41, 44–48, 51, 53]. Half of the studies conducted among prescribers (6/12) were funded by a pharmaceutical company or a lobbying organization [30, 44, 45, 48, 51, 53].

3.2 Perceptions and Experiences of Automatic Substitution of Biologics

The majority of included studies (18/27) reported negative perceptions of automatic substitution of biologics (Tables 1, 2, Fig. 2). Surveys conducted among prescribers (12/12) reported mainly negative perceptions from the study participants [30, 36, 37, 39, 44, 45, 47, 48, 51–53, 55]. Negative perceptions were reported also among pharmacists (2/5) [31, 43], patients (2/4) [32, 40], and mixed stakeholders (2/5) [41, 42]. All studies except one [46] that received funding from the pharmaceutical industry (Abbvie, Janssen, Pfizer, Sandoz) or a lobbying organization (Alliance for Safe Biologic Medicines) ($n = 9$) reported negative substitution perceptions from the participants [30, 40, 41, 44–46, 48, 51, 53].

Five studies reported positive perceptions [33, 34, 38, 49, 54] and four mixed or uncertain perceptions [29, 35, 46, 50]. Of the studies with positive findings, two surveys were conducted among pharmacists [38, 54], one among patients [49] and one interview study among various stakeholders [33]. In the only identified intervention study (no control group) [34] conducted in a hospital pharmacy, patients did not report decreased satisfaction with their medication after substitution.

Most of the identified studies measured automatic substitution-related issues by a few structured questions. In two qualitative interviews with a prospective approach (Table 2), elements required for implementing automatic substitution of biologics were identified [33, 35]. In both studies, barriers and risks related to biologic automatic substitution, such as a necessity of communication between healthcare professionals, pharmacists' competency to counsel the patient in case of a change of the administration device, and the need for a reliable pharmacovigilance system were identified. It was mentioned that to make patient- or product-specific exceptions (e.g., "dispense as written") should be possible, if needed. Substitution interval (i.e., how often the patient's medicine could be substituted) [33], clear mandate from a competent authority [35], and healthcare professionals' and patients' trust on biosimilars [33, 35] should be addressed before implementing the substitution in practice.

3.3 Quality of the Studies

Of the included surveys ($n = 23$) six (26%) [34, 38, 41, 47, 49, 50] were assessed as of high quality and six (26%) [30, 36, 44, 46, 48, 53] as of low quality (see ESM 3). The rest of the surveys ($n = 11$) were of moderate quality. The quality of the included surveys was compromised by a non-systematic approach in developing the questionnaire (22/23), which may increase a risk for ambiguous skewed questions, a lack of questionnaire testing (18/23), and potential response bias (18/23) (i.e., the risk that participants do not represent the target population or the response rate is low). The study participants did not represent the defined population of interest in the study design in 14/23 of the surveys, and the response rate was poor in 8/23 or not reported at all in 10/23 of the surveys. An accurate data collection time was missing in three surveys [46, 52, 53].

The quality of the semi-structured interviews ($n = 4$) was assessed to be appropriate for qualitative research. Interview reports lacked information on researchers' relationships with participants and the accuracy of the data collection process.

Half of the high-quality surveys (3/6) and one semi-structured interview ($n = 4$) reported mainly positive perceptions on the automatic substitution of biologics [33, 34, 38, 49].

Table 1 Included surveys ($n = 23$) according to main regional categories (Europe, North America, and other) organized by research method, year of data collection, country, the legislative status of automatic substitution at the time of the study, quality of the study, number of participants, and their perceptions/experiences of automatic substitution of biologics, and the other main outcomes of the study

Research method	Year of data collection	Country	Legislative status of automatic substitution of biologics at the time of the study[c] [12, 14, 19]	Number of participants				Medical specialty	Quality of the study[e]	Experiences and perceptions on automatic substitution of biologics, and the other main outcomes (if available)[f]		Authors [Ref.]
				Prescribers	Pharmacists	Patients	Other					
Europe												
S	2018	Spain	◆			87			High	+	Reported patient satisfaction when substituting originator prefilled syringes to pens of biosimilar etanercept in the hospital pharmacy: 23% extremely satisfied; 28% very satisfied; 23% satisfied, and 26% partly satisfied or not at all satisfied	Barbosa et al. [34]
S	2017	France	✓			629			Mod	–	3% approved substitution made by a pharmacist	Frantzen et al. [32]
S	2017	Poland	↔		260				Mod	–	17% would offer substitution of biologics	Łukasik and Nowicki [43]
S	2017	Poland	↔		61				Mod	–	23% agreed that biosimilars should be used to substitute original medicine. 75% agreed to have a doctor's permission for substitution	Pawłowska et al. [31]
S	2015–16	Ireland	**X**	102	143			De, E, G, HO, Np, Nu, R, O	High	–	<5% medical specialists considered substitution appropriate, 35–43% with physician consent. 14% of pharmacists indicated they would be comfortable with substitution	O'Callaghan et al. [41]
S	2015	France	✓		802				High	+	53% approved substitution made by a pharmacist	Beck et al. [38]
S	2015	NS	◆	118				G	Mod	–	90% disapproved substitution made by a pharmacist, 13% approved the substitution of new prescriptions	Danese et al. [37]
S	2015	France	✓	116				R	Mod	–	81% disapproved substitution made by a pharmacist	Beck et al. [39]
S	2014–15	NS	◆			383			Mod	–	1% accepted the substitution made by a pharmacist	Peyrin-Biroulet et al. [40]
S	2013	NS	◆	307				G	Low	–	64% were against automatic substitution, 18% approved substitution for new prescriptions	Danese et al. [36]
S	2013	France, Germany, Italy, Spain, UK	**✓XXXX**	470				De, E, HO, Np, Nu, R	Low	–	95% considered from very to somewhat important to have sole authority to decide the biologic product	Dolinar and Reilly [30]

Table 1 (continued)

Research method	Year of data collection	Country	Legislative status of automatic substitution of biologics at the time of the study[c] [12, 14, 19]	Number of participants				Medical specialty	Quality of the study[e]	Experiences and perceptions on automatic substitution of biologics, and the other main outcomes (if available)[f]	Authors [Ref.]
				Prescribers	Pharmacists	Patients	Other				
North America											
S	2016-17	USA (States NS)	◆	297				De, G, R	Low	– 17% would be comfortable with pharmacy-level substitution without physician knowledge	Teeple et al. [44]
S	2015	USA (National, District of Columbia, Florida, North Carolina, Maryland, Pennsylvania)	◆◆✓XXX	97				De	Mod	– 94% considered it very or somewhat important that the prescriber should have control. 88% considered that substitution would occur in the future	Barsell et al. [45]
S	2014	Canada	X	81				R	High	– 88% would feel concerned or very concerned if substitution were possible	Grabowski et al. [47]
S	2014[a]	USA (States NS)	◆				8[d]		Low	? Half of the participants were reluctant to initiate the practice of automatic substitution	Cohen et al. [46]
Other											
S	2019	Pakistan	◆		305				High	? 59% neither agreed or disagreed with statement "Being a pharmacists, I can safely switch to biosimilar without physician permission" (8% agreed or strongly agreed; 32% disagreed or strongly disagreed)	Shakeel et al. [50]
S	2018[a]	Tunisia	X	107				HO	Low	– 52% were in favor of a justified substitution and interchangeability, 4% were in favor of a systematic substitution, 7% were in favor of systematic interchangeability, 23% against substitution and interchangeability	Hadoussa et al. [52]
S	2017–18	Australia	✓			132			High	+ 25% were worried about pharmacist-led substitution without consulting the prescriber	Kovitwanichkanont et al. [49]
S	2017	Korea, Japan, China, other Asian countries	◆◆◆◆	151				G	Mod	– 87% disagreed with the automatic substitution of the originator with a biosimilar by a pharmacist. 44% disagreed with automatic substitution in any case. Disagreement was highest among prescribers in Korea (62%)	Park et al. [55]

Table 1 (continued)

Research method	Year of data collection	Country	Legislative status of automatic substitution of biologics at the time of the study[c] [12, 14, 19]	Number of participants				Medical specialty	Quality of the study[e]	Experiences and perceptions on automatic substitution of biologics, and the other main outcomes (if available)[f]	Authors [Ref.]
				Prescribers	Pharmacists	Patients	Other				
S	2016	France and Canada	✓**X**		229				Mod	+ 25% considered that only physicians could proceed with the interchangeability of biosimilars	Ade et al. [54]
S	2016	Russia[b]	◆	206				G, HO, R	Mod	– 53% were negative, 25% were neutral and 22% were positive about substitution	Karateev and Belokoneva [51]
S	2016	Australia	✓	160				De, E, HO, G, Np, Nu, R	Low	– 90% considered it critical or very important to have sole authority to decide the biological product. 51% did not accept substitution for patients with chronic disease. 53–81% of respondents considered that clinical trial data on safety and efficacy after switch(es) is suitable evidence demonstrating that biosimilar is suitable for substitution on pharmacy level	Murby and Reilly [48]
S	2015[a]	Argentina, Brazil, Colombia, Mexico	◆**XXX**	399				De, E, HO, Np, Nu, R, O	Low	– >80% considered it critical, or very important to have sole authority to decide the biological product	Gewanter and Reilly [53]

De Dermatology, *Di* Diabetes, *E* Endocrinology, *G* Gastroenterology, *HO* Hematology/Oncology/Medical oncology, *NS* Not specified, *Np* Nephrology, *Nu* Neurology, *O* Other, *R* Rheumatology, *S* Survey

[a]Manuscript submission year (if data collection time was not indicated)

[b]Not following the European legislation on biosimilars, thus categorized in 'Other'

[c]Legislative status does not indicate if the substitution practice is implemented. ✓ Substitution is allowed in some circumstances, ↔ Substitution is not specified/not specifically prohibited, **X** Substitution is not allowed, ◆ Information is not available in consulted sources

[d]Payers

[e]Quality evaluation, please see Electronic supplementary material 3. *High* high quality, *Mod* moderate quality, *Low* low quality

[f]+ Perceptions mainly positive, **?** Uncertain /mixed perceptions, – Perceptions mainly negative

Table 2 Included semi-structured interviews ($n = 4$) organized by research method, year of data collection, country, the legislative status of automatic substitution at the time of the study, quality of the study, number of participants, and their perceptions/experiences of automatic substitution of biologics, and the other main outcomes of the study

Research method	Year of data collection	Country	Legislative status of automatic substitution of biologics at the time of the study[a] [12, 14, 19]	Number of participants				Medical specialty	Quality of the study		Experiences and perceptions on automatic substitution of biologics, and the other main outcomes (if available)[g]	Authors [Ref.]
				Prescribers	Pharmacists	Patients	Other					
Europe												
I	2018	Finland	↔	7[b]	9[b]	2[b]	14[c]	NS	Not scored	+	50% had a positive attitude to substitution, 25% suggested that risks should be solved before implementing the substitution, 25% deemed substitution as an inappropriate model. Treatment-naïve patients were suggested the most suitable for substitution Several benefits and risks related to automatic substitution were identified. For risk management, administration device counseling by a pharmacist, substitution interval, communication between healthcare professionals, and further training of healthcare professionals on biosimilars were identified as important among other measures	Tolonen et al. [33]
I	2017–18	Austria, Belgium, Croatia, Denmark, France, Ireland, Italy, Malta, Poland, Portugal, Netherlands, UK, Spain, Switzerland, and pan-European perspective	◆	9	10	9	16[d]	E, G, HON, R	Not scored	?	Both emotional (lack of trust and experience, loss of prescriber's control over treatment, fragile landscape regarding biosimilars) and practical (no pharmacists' mandate to substitution, insufficient communication systems between prescriber and pharmacist) barriers were identified Most prescribers and pharmacists were not against pharmacist substitution providing the prescriber is informed about change and the treatment is under prescriber's control, but it was noted that participants disagreed over future automatic substitution. Addressed barriers, patient- and product-specific exceptions, and an efficient system for reporting adverse events are needed to organize substitution in practice in the future	Barbier et al. [35]

Table 2 (continued)

Research method	Year of data collection	Country	Legislative status of automatic substitution of biologics at the time of the study[a] [12, 14, 19]	Number of participants				Medical specialty	Quality of the study	Experiences and perceptions on automatic substitution of biologics, and the other main outcomes (if available)[g]		Authors [Ref.]
				Prescribers	Pharmacists	Patients	Other					
I	2017	UK	**X**	11	4		7[e]	Di, G, R	Not scored	–	The majority of participants had a negative attitude. A minority of the participants considered that substitution may occur in the future	Aladul et al. [42]
I	2012–13	Belgium	**X**	2	3	1	13[f]	NS	Not scored	?	Biosimilar substitution was considered more acceptable for treatment-naïve patients	Dylst et al. [29]

Di Diabetes, *E* Endocrinology, *G* Gastroenterology, *HO* Hematology/Oncology/Medical oncology, *I* Semi-structured interview, *NS* Not specified, *Np* Nephrology, *R* Rheumatology

[a]Legislative status does not indicate if the substitution practice is implemented. ✓ Substitution is allowed in some circumstances, ↔ Substitution is not specified / not specifically prohibited, **X** Substitution is not allowed, ◆ Information is not available in consulted sources

[b]Number of interviews

[c]Interviews with authorities ($n = 7$), representatives from industry and wholesalers ($n = 6$), nurses ($n = 1$)

[d]Nurses ($n = 9$), regulator ($n = 7$)

[e]Nurses

[f]Authority ($n = 4$), academic ($n = 3$), industry ($n = 6$)

[g]**+** Perceptions mainly positive, **?** Uncertain /mixed perceptions, **–** Perceptions mainly negative

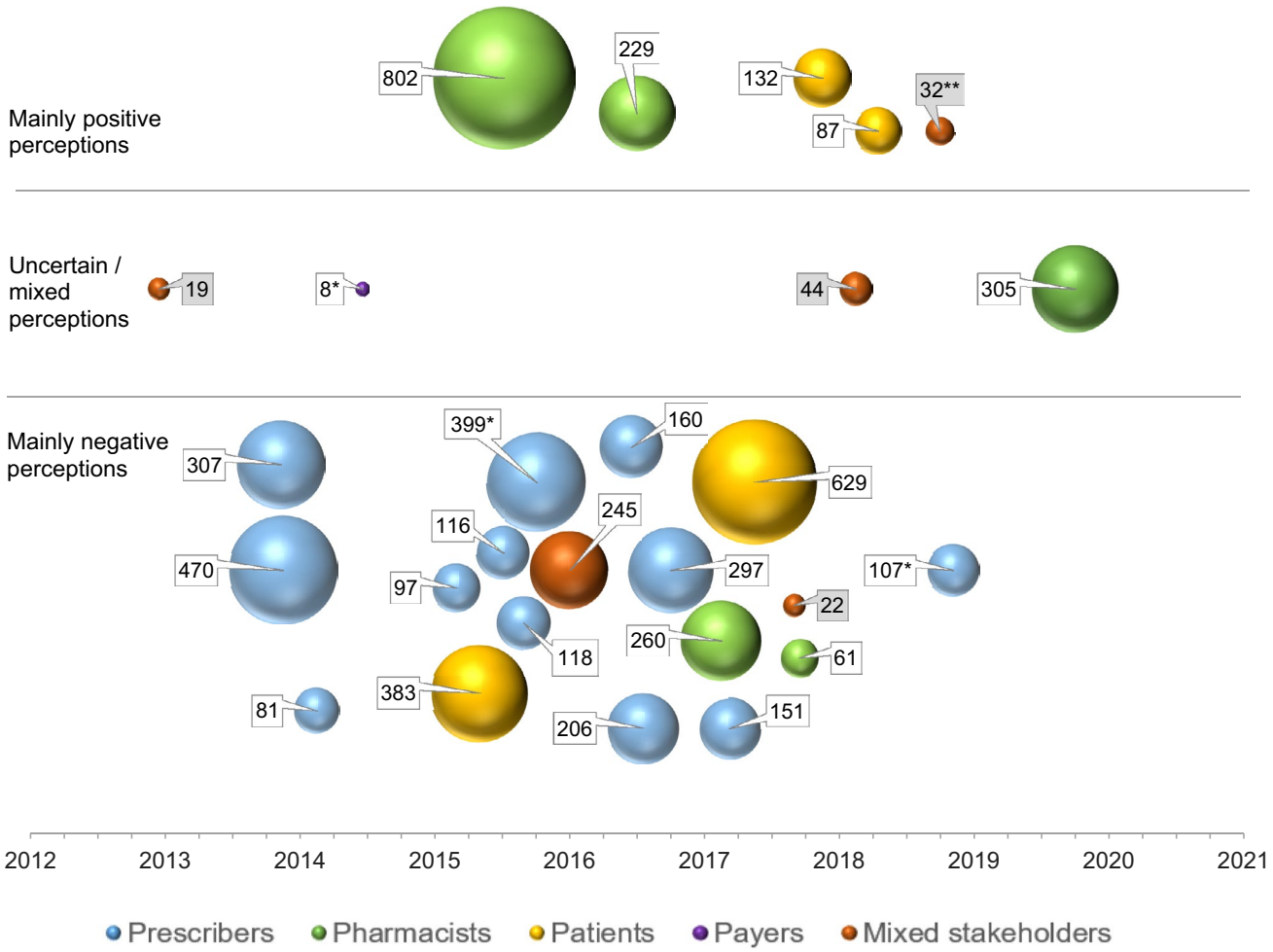

Fig. 2 The summary of included studies (n = 27). Each bubble describes one study. The bubble is centered in the middle of the data collection period as per year (*data collection time was not reported; bubble is centered by the date of manuscript submission). The color of the bubble indicates the type of participants as prescribers (n = 12), pharmacists (n = 5), patients (n = 4), payers (n = 1), and mixed stakeholders (n = 5). The area of each bubble and the included numeric value describe the number of study participants (**units of analysis). White and grey backgrounds indicate the study type as surveys and interviews, respectively. The bubble is located in one of three segments depending on the perceptions of the participants on the automatic substitution of biologics

4 Discussion

Despite the importance of biologics including biosimilars in modern pharmacotherapy and the societal need to control increasing healthcare expenditures, few studies were found on pharmacist-led automatic substitution of biologics. Although the literature search was not limited by study design, methods, or settings, only 27 full-text, peer-reviewed studies were identified. The majority were surveys or opinion polls of low (n = 6) or moderate (n = 11) quality. Only one study applied intervention design, the impact of which was assessed using a survey [34]. None of the identified studies assesses the safety and effectiveness of implementing automatic substitution in practice, which may be explained by the fact that automatic substitution is largely not practiced or allowed for biologicals [10, 12]. However, in two studies [33, 35], risks and barriers in implementing automatic substitution was prospectively identified. It is obvious that available evidence is not rigorous enough to draw any conclusions on the automatic substitution of biologics. Therefore, more research on how to organize automatic substitution of biologics that applies robust scientific methods is needed for decision making.

The identified negative perceptions of automatic substitution of biologics may reflect the respondents' general mistrust of biosimilars. In the Australian study, prescribers considered that suitability of a biosimilar for automatic substitution can be demonstrated in clinical trials related to safety and efficacy of prescriber-led switching [48]. According to recent systematic reviews, stakeholder perceptions

of biosimilars are largely cautious and their knowledge on biosimilars is scarce [8, 10]. The fact that automatic biologic substitution is generally not allowed may increase negative perceptions. On the other hand, this mistrust can be intentionally generated or enhanced by the opinion polls to influence market shares of biologics and their biosimilars. Feeding the ongoing debate with evidence from opinion polls indicating that physicians are against the substitution may be powerful. Potential risks related to the interchangeability of biosimilars and their reference medicines have been used often as an argument in scientific debate [21, 56]. However, no evidence has been found to support the assumption that a switch between biological medicine and its biosimilar has a negative impact on the efficacy, safety, or immunogenicity of the biological treatment [56, 57]. Therefore, a physician-led switch is already widely supported by national regulatory agencies and medical associations [21, 58].

Creating evidence and awareness that physicians dominantly have negative perceptions of the automatic substitution of biologics may influence public opinion, particularly the opinions of patients receiving treatment with biologics including biosimilars. These perceptions may reinforce the nocebo effect; that is, patients' negative beliefs can induce adverse events or other unwanted treatment outcomes [59], which in prescriber-led switching can be managed by shared decision making between a prescriber and a patient [60]. However, there are also other potential methods to minimize nocebo effects [61, 62], which may be appropriate when considering automatic substitution. Current negative perceptions may be amplified by opinion-poll-type studies, and thus such studies have been biased in this respect, highlighting a need for further rigorous research. Studies on practices and strategies for safely implementing the automatic substitution of biologics are especially needed. In our systematic review, we found only one prospective study carried out in Finland to prepare for the national implementation of automatic substitution of biologics [33], and one European study identifying prerequisites for automatic substitution of biologics [35]. No research was found on the safety and effectiveness of actual substitution practices.

The negative and suspicious perceptions concerning the automatic substitution of biologics seem to follow the same pattern seen previously with the generic substitution of small-molecule medicines [63]. Although the substitution of biologics is not fully comparable to that of small-molecule chemical drugs, the experiences of implementing generic substitution could be useful when carrying out the change allowing automatic substitution of biologics by their biosimilars. As we know today, generic substitution has become a widely recognized and implemented procedure providing significant direct drug cost savings to medicine users and public budgets, especially if combined with the reference price system [64–66].

Our findings reflect the fact that automatic substitution practices are largely not allowed or implemented across Europe and other regions of the world. Further, the concept of automatic substitution varies between different jurisdictions [67]. While the EU remits the decision on interchangeability and its practical execution to each Member State, in the US, automatic substitution is only possible for interchangeable biosimilars. To gain the interchangeability designation, additional clinical data to demonstrate stability in clinical performance, pharmacokinetics and immunogenicity profile during multiple switches is needed for a biosimilar [68]. Thus, although the US has the legal framework to implement automatic substitution of biological drugs, it is possible that the first efficient substitution implementations will be seen through national decision making in the EU. Preconceived processes to ensure medication safety, and stakeholders' confidence in interchangeability are imperative when implementing automatic substitution of biologics [33, 35], highlighting a need for sound and comprehensive post-marketing monitoring [69].

The present systematic review applied a robust scientific method to collect comprehensive evidence on automatic pharmacist-led substitution of biologics. The strength of the study was that two library information specialists participated in designing the search queries. Two researchers screened and selected the articles, and the quality of the included surveys was systematically assessed. The major limitations concern the amount and quality of research evidence found. The research evidence is mainly based on surveys of low to moderate quality without generalizable results due to convenience sampling and small sample sizes not representing the populations of interest. The applied survey instruments and measures were not tested or validated, and most of the studies did not have the automatic substitution of biologics as their primary objective. The level of evidence generated in this type of primary study is low or very low [70, 71]. Further, the healthcare systems in different countries and continents vary, allowing for various local combinations of physician-led switch and pharmacist-led automatic substitution. For example, biological medicines may be dispensed from a hospital pharmacy instead of a community pharmacy, and the transition from biologic to another interchangeable biologic may be coordinated by a multidisciplinary healthcare team. In the identified intervention study [34], prescribers informed the patients on upcoming transition, and a substitution practice was conducted in a hospital pharmacy. On the other hand, these differences in organizing the substitution and variations in the prescriber's participation in the transition procedure may help to find the optimum future procedures for safe automatic substitution practices while substitution in community pharmacies is not widely allowed.

The attitudes of prescribers, other healthcare professionals, and patients significantly influence the deployment of biosimilars. The conflicting perceptions on this issue indicate the prevailing need for consistent and objective information on biosimilars' quality, efficacy, and safety. There is also an urgent need for robust, scientifically valid, and generalizable studies on the practices of automatic substitution of biologics. Deployment of simulations, pilots, intervention studies with control groups, economical evaluations, and research applying different study designs are needed on the topic to gain sound evidence for policy making.

5 Conclusion

This systematic review indicates a lack of research evidence and experience on the automatic substitution of biologics. Even though automatic substitution of biologics has been suggested to be a potential strategy for controlling growing healthcare costs, the identified evidence is mainly based on opinion polls and surveys of low or moderate quality, yielding results that are neither generalizable nor suitable for guiding policy making. Policy makers should be aware that no robust evidence on how to implement automatic substitution for biological medicines is available. Studies on practices and strategies for safely implementing substitution are needed. This type of research study should go hand in hand with changes from the policy side, which in turn can stimulate further research in this area.

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Declarations

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Conflict of interest One of the included studies in this systematic review was authored by Tolonen et al. [33]. However, it was analyzed by the same criteria as other included studies. Hanna M. Tolonen has participated in a congress for which a participation fee was sponsored by Roche Oy. Jenni Falck, Pekka Kurki, Päivi Ruokoniemi, Katri Hämeen-Anttila, Kenneth M. Shermock, and Marja Airaksinen declare that they have no other competing interests related to this study.

Availability of data and material All the materials relevant to this systematic review are included in the article, fully referenced, or provided as electronic supplementary material.

Ethics approval Ethical approval was not applicable for this systematic review.

Consent Consent was not applicable for this systematic review.

Authors contributions All authors contributed to the study conception and design. HMT and JF performed the search and evaluation of the literature. HMT performed data extraction, analysis, and quality assessment, and all authors carefully reviewed them. HMT wrote the first draft of the manuscript, and all authors participated in critical revision of subsequent versions of the manuscript. All authors read and approved the final manuscript.

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