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Systematic Literature Review

Real-World Evidence in Healthcare Decision Making: Global Trends and Case Studies From Latin America

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ABSTRACT

Background: Real-world evidence (RWE) is increasingly used to inform health technology assessments for resource allocation, which are valuable tools for emerging economies such as in America. Nevertheless, the characteristics and uses in South America are unknown.

Objectives: To identify sources, characteristics, and uses of RWE in Argentina, Brazil, Colombia, and Chile, and evaluate the context-specific challenges. The implications for future regulation and responsible management of RWE in the region are also considered.

Methods: A systematic literature review, database mapping, and targeted gray literature search were conducted to identify the sources and characteristics of RWE. Findings were validated by key opinion leaders attending workshops in 4 South American countries.

Results: A database mapping exercise revealed 407 unique databases. Geographic scope, database type, population, and outcomes captured were reported. Characteristics of national health information systems show efforts to collect interoperable data from service providers, insurers, and government agencies, but that initiatives are hampered by fragmentation, lack of stewardship, and resources. In South America, RWE is mainly used for pharmacovigilance and as pure academic research, but less so for health technology assessment decision making or pricing negotiations and not at all to inform early access schemes.

Conclusions: The quality of real-world data in the case study countries vary and RWE is not consistently used in healthcare decision making. Authors recommend that future studies monitor the impact of digitalization and the potential effects of access to RWE on the quality of patient care.

Keywords: big data, epidemiology, health policy, health technology assessment, Latin America, real-world evidence.

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Introduction

Healthcare decision makers, the pharmaceutical industry, patients, and clinicians are increasingly using "real-world" data to assess the safety, effectiveness, and costs of interventions.[1,2] *Real-world data* (RWD) refer to healthcare delivery data that are routinely collected from sources such as providers' paper or electronic health records, billing data, clinical registries, surveys, and surveillance data from healthcare activity.[2] *Real-world evidence* (RWE) is derived from the analysis of RWD and refers to the clinical evidence of a medical product's benefits and risks, safety, and effectiveness.[2] It is used globally to complement data from randomized controlled trials (RCTs), for example, when assessing the cost effectiveness and safety of interventions in clinical practice, enabling the generalization of clinical findings to a more inclusive and larger population.[1]

It has long been recognized that evidence from RCTs is insufficient when used as the sole basis for coverage or decision making in healthcare.[1,3] Although clinical efficacy can be demonstrated using RCTs, required length of trials, the exclusion of major population subgroups, and its costs render them controversial as the only basis of evidence for health technology assessments

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(HTAs).[1,4] To complement RCT data, regulators such as the Food and Drug Administration in the United States and the European Medicines Agency have been gradually incorporating the use of RWE to assess the value of new interventions and monitor their safety and effectiveness after approval for clinical use.[2,5–7] This is often a condition for early authorization or fast-track approval of treatments that fulfill major unmet medical needs, address key public health issues, or pertain to rare diseases.[8] The healthcare sector is increasingly willing to accept less certainty in treatment effectiveness in return for fast patient access to innovative treatments.[8,9] In return for initial licensing for a specific patient population on the basis of limited clinical data, research institutions and pharmaceutical companies are becoming more advanced in mining data to monitor and evaluate the safety and effectiveness of their interventions to reduce uncertainty in the postmarketing authorization phase.[9]

In contrast, emerging economies rarely capture transferrable and reliable RWE that can be used by regulators or for HTA decision making. Regions such as Latin America, Asia Pacific, and Africa tend to have significant unmet medical needs, major public health issues, and populations with a high burden of communicable and chronic diseases. This might lead to potential health outcome benefits and cost savings derived from the introduction of RWE to inform resource allocation and fast-tracked regulatory and coverage decisions.

The healthcare sector in Latin America is transforming. In recent years, the region has recorded an increase in healthcare spending,[10] expanded health coverage, and launched several successful public health initiatives across the region.[11] Although there is an increasing aging population and the region is experiencing an epidemiological shift from infectious to chronic diseases, health outcomes and life expectancies are improving dramatically.[11,12] HTA agencies and regulations have emerged across the Latin American countries to contain the increasing costs of public healthcare by improving the allocation of limited resources. Nevertheless, reliable and robust sources for RWE are few, so local decision makers are reluctant to tolerate the risk of selection bias, uncontrolled confounding, and endogeneity derived from unreliable RWD. Furthermore, if their internal capabilities to apply highly sophisticated analytical methods are limited, RWE is even less valued. Thus, HTA evaluations continue to rely solely on data from RCTs conducted abroad as the basis for decision making. Although some reimbursement schemes for high-cost treatments require applications supported by RWE, it has not yet been harnessed and applied by either public or private sector stakeholders to its full potential.

Despite these limitations, Latin America has recently seen a surge of interest in RWE, with an increasing number of academics and pharmaceutical companies seeking access to or creating databases and registries to inform HTA submissions and best practices in the healthcare sector.[11] This study presents the sources and uses of RWE in 4 South American countries, Argentina, Brazil, Chile, and Colombia, with an evaluation of the context-specific challenges of data generation and limitations of the healthcare system infrastructure. Finally, this study considers the implications of this research for future regulation and responsible management of RWE in South America.

Methods

We performed a systematic literature review, a database mapping, and a targeted search in the gray literature and the websites of governments and relevant public agencies. In addition, we developed a series of RWE workshops in Argentina, Brazil, Chile, and Colombia where we consulted key opinion leaders (KOLs) and validated information previously collected through the review. These half-day workshops included 3 presentations, each followed by a discussion session, and were attended by various local stakeholders including representatives of the Ministries/Secretaries of Health, public/private health maintenance organizations, physicians engaged in outcomes research, statistics departments, and so forth. Additional information on the workshops can be found in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.01.014.

A systematic search was run in the LILACS, MEDLINE, and CAB Global Health databases to identify sources of RWD and assess the availability and characteristics of RWE in Latin America. The search strings included the following terms: "observational" or "non-interventional" or "retrospective" or "cohort" or "survey" or "cross sectional" or "dataset" or "real world" data in Latin America and the 4 case study countries (see full search string in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.01.014). The articles were screened for relevance and they were excluded if the target population did not include Argentinian, Brazilian, Chilean, and/or Colombian patients; if the outcomes were not health-related; and if the study design was a clinical trial, literature review, feasibility analysis, or meta-analysis. Reason for exclusion was recorded and, for those included, basic information pertaining to the data source used was extracted (name, geographic coverage, indication, and type of data). The identified sources of RWD were de-duplicated and categorized into the following 3 database types: (1) administrative databases, (2) clinical and patient registries, and (3) national health information systems including surveillance.

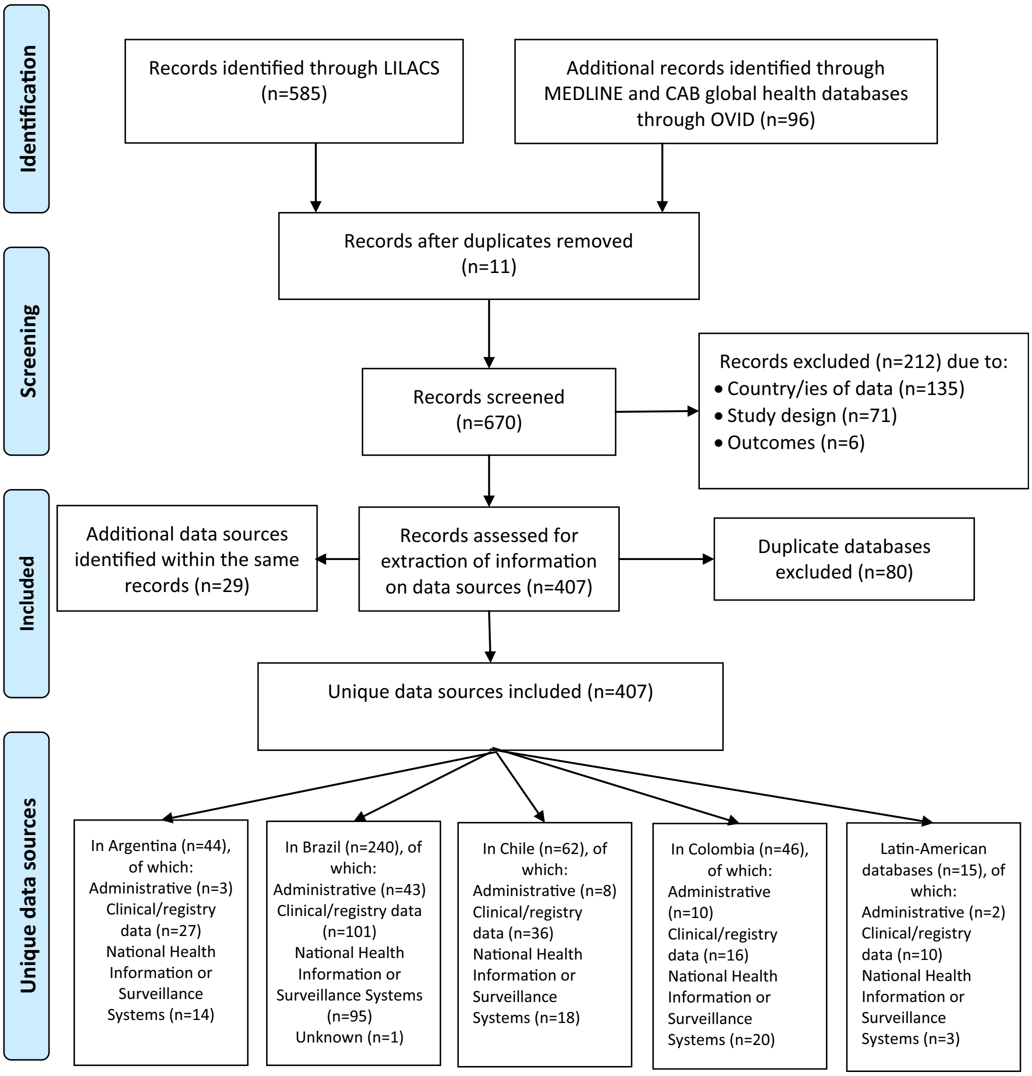
KOLs were consulted on the generation and uses of RWE in their respective countries to validate the findings of the literature search, to identify the challenges of incorporating RWE into healthcare decision making, and finally to ascertain areas of opportunities. To supplement KOL contributions, a targeted literature review was conducted with a focus on health policy in Argentina, Brazil, Colombia, and Chile. Gray literature, peer-reviewed articles, and online sources were reviewed from societal, clinical, and industry perspectives. Search terms for this part of the investigation were the following: "real-world data," "real-world evidence," "early-access programs," "health technology assessments," "health economic evaluations," "expanded access programs," "performance-based risk-sharing agreements," "compassionate use programs," "managed-entry agreements," "conditional reimbursement agreements," "coverage with evidence development," and "pharmacovigilance." The authors scanned and categorized the contents into 3 main findings alongside KOL contributions: (1) the generation of RWE from secondary sources: administrative, registry/clinical, and national health information systems; (2) the uses of RWE for pharmacovigilance, the monitoring of safety, and drug utilization, as well as HTA assessments; and (3) the methodological challenges of using RWE in practice.

Results

Sources of RWD in Latin America

Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram for the systematic literature review (see Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.01.014 for additional information). Searches of the LILACS, MEDLINE, and CAB Global Health databases retrieved 681 potentially relevant publications from the case study countries (Argentina, Brazil, Chile, and Colombia), of

Figure 1. Database mapping flow diagram.



Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group (2009).[13] PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

which 11 were removed because of duplication. Of the remaining 670 studies, 487 were found to be based on relevant sources of RWD. The remaining 212 studies were excluded on the basis of study design (n = 71), geographic coverage (n = 135), and non–health-related outcomes (n = 6).

In the 487 articles screened for abstraction, 407 unique data sources were identified after identifying multiple data sources within articles and de-duplicating databases (n = 80). It was found that most databases had a population coverage of 1 hospital or county (n = 201), and that fewer studies cited data sources with national (n = 105) or regional (n = 75) coverage. The least common were international databases (n = 24). Databases were categorized into types, with clinical databases (including electronic medical records [EMRs]) or patient registry databases being the most common (n = 190), health information systems (including surveillance systems) being the second most common (n = 101), and finally administrative databases being the scarcest (n = 66).

Most unique databases that were identified in the search covered the Brazilian population (n = 240), followed by Chilean (n = 62), Colombian (n = 46), Argentinian (n = 44), and general Latin American (n = 15) databases. The most common studied outcomes were hospital-related infections and treatment-related adverse events (pharmacovigilance) (13%), followed by cardiovascular diseases (11%), oncology (11%), hospitalizations, surgery, and emergency care data (8%), maternal and newborn health (7%), tuberculosis and other respiratory diseases (5%), and sexually transmitted diseases including HIV/AIDS (4%).

Input from KOLs and targeted literature searches informed definitions of database types as follows. First, administrative databases are classified as data repositories managed at a regional or organizational level to capture process indicators from reimbursement, facility, or insurance data.[3] They are used to assess the economic impact of treatments using cost data.[11] Second, health information systems are public health surveillance systems characterized by the ongoing and systematic monitoring of health events to reduce morbidity and mortality.[13] They typically monitor key health indicators such as disease prevalence, burden, and services utilization. Outputs can be used to inform national and provincial ministries of health (MoH) on the needs of healthcare services, and the resulting health statistics are disseminated for public access on an aggregated level. Finally, clinical and patient registries consist of observational cohort studies for a disease or treatment group, and are typically used for understanding the natural history of diseases or monitoring the associated care quality, provider performance, or cost effectiveness.[3] Table 1 presents the distribution and types of RWE available in the 4 South American case studies. Table 2 presents detailed information on 4 examples per country, for example, promising initiatives to create interoperational national health information systems, a selection of condition-specific clinical databases, EMR systems, and finally an example of maternal and neonatal databases that typically combine administrative and clinical data, although with limited depth.

Uses of RWE

During the desk research phase, we identified 4 major uses of RWE globally: (1) regulatory processes such as marketing authorization, early access schemes, and pharmacovigilance; (2) HTA decision making; (3) academic research; and (4) healthcare management and financing.

Table 2 presents the current use of RWE in South America, or lack thereof, following this taxonomy. We found that in the countries under study, regulators mainly use RWE for pharmacovigilance purposes. Pharmacovigilance and technovigilance of pharmaceutical products and devices are informed by real-world surveillance of adverse events and treatment patterns. The case studies demonstrate variation between countries' pharmacovigilance regulations that apply, with Argentina's National Administration of Drugs, Food and Medical Technology legislation requiring "corrective procedures" and Chile's National Drug Regulations Agency's interest in building "safety profiles" using RWE for authorized drugs.

Nevertheless, there is limited use of early access schemes for treatments that meet unmet needs or to obtain historical comparators for the assessment of orphan indications. Although pharmaceutical producers in the European Union and the United States can apply for early access, through Adaptive Pathways (European Union) or Breakthrough Therapy (United States) designation, by agreeing to collect postauthorization RWE in exchange for early authorization of a treatment, this strategy is not used in South America where phase III RCTs are deemed to be the criterion standard for marketing authorization. A rare exception is the occasional approval of Compassionate Use Programs, although no RWD are collected for secondary use.

Although RCTs are considered the criterion standard for HTA submissions, there is a growing recognition that observational data are a key tool for budget impact analyses and economic evaluations in all South American countries (see Table 2). Across South America, payers and producers of biopharma and medical devices are using economic and effectiveness RWE to support price and coverage negotiations. Nevertheless, these are exceptions and are typically implemented in small populations by the private sector and are hardly ever outcomes-based. In Brazil, for instance, although access to RWE is limited by a lack of interoperability between regional and organizational systems, there is high use of RWE among HTA agencies. For example, RWE, domestic or international, was included in 88.2% of HTA submissions between 2011 and 2014.[14] Elsewhere in Argentina, Colombia, and Chile, economic evaluations and cost-minimization analyses are being conducted to support coverage decisions. Nevertheless, the use of RWE in South America tends to be part of the value argumentation of pharmaceutical products, and they are generally not part of the binding market access agreements between healthcare payers and pharmaceutical producers.

Academic institutions in South America use RWE to address transferability to wider populations in the region. These, in turn, are used in economic model adaptations for HTA submissions. Academic institutions also conduct epidemiological research on mortality, incidence, and prevalence of diseases on the basis of national surveillance data to inform healthcare management and innovation. Institutions across South America are responsible for the national or regional disease-specific registries that were started as an individual initiative for self-contained research projects. Academic and governmental partnerships have also been set up to monitor the performance of the national healthcare system, improve health outcomes, and monitor out-of-pocket expenses. For instance, Chile's MoH has begun to digitalize databases, synchronize systems, and collect routine population data. Also, Argentina's Plan Nacer is a government-funded auditing program to monitor quality and allocation of resources in clinics treating uninsured women and children. In exchange for funding, clinics across Argentina contribute to a surveillance network for maternal and newborn health outcomes.

Challenges and Opportunities in the Collection and Consolidation of RWE

The identification of challenges and opportunities is based on KOL inputs, the proceedings of the discussions during the workshops, and insights from the literature pertaining to the limitations of the studies reviewed. Although they are multiple and diverse, there are some common challenges to overcome, as summarized herein.

- *Problems with the data:* There is a wide variety of available data across all South American countries. Nevertheless, countries face the key challenges of data integrity, quality, and security. National variations in data collection and patient concerns in sharing data pose a serious challenge to gathering meaningful insights from data.
- *Gaps in expertise:* The KOLs from Brazil, Chile, and Colombia pointed out that the number of skilled personnel is insufficient to analyze the large volume of data that have, and will, become available. To benefit from RWE, all interested parties must address this gap and engage in training and capacity building.
- *Lack of confidence in observational research:* To capture reliable and transferrable RWE for policy making and HTA decisions, observational research must follow good practices as highlighted in the International Society for Pharmacoeconomics and Outcomes Research Special Task Force Report on Real-World Evidence in Health Care Decision Making. Studies should be fully transparent and should take steps to resolve validity issues of confounding, measurement error, selection bias, and missing data.[15] The aforementioned gaps in expertise and problems with the data foster a conservative attitude from the decision makers toward RWE.
- *Trust issues between users and data holders and among the latter themselves:* There is a limited, not-always transparent, and complex collaboration of various parties (industry, academia, hospitals, government, and payers). Data security issues and limited access affect the opportunities to analyze the data and use the knowledge. In turn, this reinforces another difficulty regarding the longitudinal follow-up of patient pathways through the different healthcare services. We have not identified any data aggregation platforms in the region, which speaks about the impaired cooperation.

Table 1. Summary of health information systems and national health data in 4 Latin American countries.

National Health Information Systems				
Information	**Argentina (SISA)**	**Brazil (DATASUS)**	**Colombia (SISPRO)**	**Chile (SIDRA)**
Objectives	• To improve patient care and health system decision making among all stakeholders • Optimize information management, using a single national health information system[16]	• To control payments to public and private service providers for the SUS[1] • Collect, process, and disseminate healthcare and demographic data	• Informed decision making, policy support, regulatory monitoring, and service management[17]	• To create a national repository of health information and common EMRs
Summary	• Quick and reliable sharing of information to control validation, integrity, security, and availability • Link human resources and streamline services through an integrated database and a decentralized management system • Argentina's national health surveillance system, mortality statistics, and national hospital discharge records used to monitor history of diseases and for health policy planning such as assessing the economic impact of immunization strategies[18,19]	• Data include indicators, services, and products consumed as well as estimates of mortality and morbidity across specific populations • Developed >200 information systems to better inform the MoH and the state and municipal secretaries of health • Examples of the uses of DATASUS are to access *ICD* codes, use of burns facilities, and the risk factors for tuberculosis in remote regions[20,21]	• Data include patient characteristics, health insurance coverage (contributed or subsidized), healthcare facility main diagnosis, intervention, length of stay, and condition when discharged • Colombian MoH and Social Protection Register consolidate data from the healthcare services using *ICD-10* codes[22] • Covers the population that uses services within the Social Security Health System[23] • Data are subject to continuous quality control testing • SISPRO has been used to analyze healthcare access and causes of death, as well as to monitor the rates of domestic violence and drug interactions[24–26]	• An integrated information system that connects primary with the secondary and hospital-level care • Provides longitudinal data about care supplied in the health system, but also about patient outcomes • SIDRA project aims to report on the living conditions of immigrants, disease-specific hospital resource use, and incidence rates of different diseases[27–29] • The hospital discharge database is a country-wide hospitalization census • Data on utilization of services in the public (REM) and private sector (REMSAS) are available from the Department of Statistics in the MoH[30]
Data use by third party	• Free public access • Access with required registration (multiple levels of data access/management)[16]	• Free access to information using National Health Cards • Restricted access to personal health records (using a card and password). Physicians can access examination results, medical procedures, and medicines purchased[31]	• SISPRO offers patient-level nationwide data that are used across the Latin American region. Access is free of charge following registration process and online training for the different modules with information on affiliation, diagnosis, hospital services, and medicines among other types of data[23]	• EHRs to be accessible to all Chilean healthcare providers[32]
Limitations/challenges	• Not yet fully implemented, still in the planning phase • Managing the various health system resources, interests, and capacities • Surviving management/political changes—key factor for long-term projects • Prioritizing overall benefit rather than particular interests[16]	• Longitudinal follow-up of individual patients hampered by the need to use probabilistic matching in the absence of a unique identifier • Cannot be used to characterize the healthcare system as a whole • Limited by incompatible data and lack of common definitions of healthcare indicators • Lack of incentives for routine data collection; some patient encounters are missed and data quality varies	• The accuracy of diagnoses has been questioned • Data tend to be of higher quality for high-cost diseases (or procedures) because data collection depends on reimbursements[33] • Overlapping or lack of integration of different data sources collecting similar or complementary information, ie, Registries from the National Cancer Institute, the National Health Institute, *Cuenta de Alto Costo*, etc	• Lack resources to unify national information systems • Compatibility issues from local health systems operating own information systems pre-SIDRA • Synchronizing records, processes, and information systems is a challenge • Supplying resources to cover transaction costs associated with system migrations is a challenge

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Table 1. Continued

Disease- and condition-specific clinical registries

Argentina	Brazil	Colombia	Chile
• Immunization registry • Blood donor registry • Cancer drug bank registry • National school health registry • Chronic kidney registry • Cardiovascular registry • Hearing aid care registry • HIV-AIDS patient management system[16] • National stroke registry (ReNACer)[34]	• HIPERDIA: hypertension and diabetes—ensures that demographic, epidemiological, morbidity, and mortality data on patients are accessible • Stroke prevention in atrial fibrillation therapy monitor • National health and wellness survey • Kidney transplant registry, Sao Paulo[35]	• Vaccine-preventable disease registry • Vector transmitted registry • Sexually transmitted disease (including HIV/AIDS) registry • Accident registry • Intoxication registry • Chronic disease registry • Organ transplant registry[36] • Tuberculosis surveillance database[37] • Surveillance system for domestic violence (SIVIF)[26] • *Cuenta de Alto Costo* has long-term information and follow-up for renal disease, HIV, and cancer	• Immunization registry • Blood donor registry • Cancer drug bank registry • National school health registry • Chronic kidney registry • Cardiovascular registry • Hearing aid care registry • HIV-AIDS patient management system[16] • National stroke registry (ReNACer)[34]

EMR systems

	Argentina (*Hospital Italiano de Buenos Aires*)	Brazil (health national cards)	Colombia (*Salud Total* and *Sura*)	Chile (*Mas Salud Occidente*)
Summary	• Private sector hospital with exemplary health information system • Sophisticated coding system for hospitalizations and prescriptions • Facilitates cohort studies[38]	• In 2011, the MoH launched a strategy to register all Brazilians to either a public or a private healthcare system[39] • The SUS national health card is used to register all citizens' diagnoses, prescriptions, and hospitalization history	• EMRs exist but they are not integrated, because they have been developed and adopted by different HMOs and healthcare institutions • Large hospitals host clinical and cost EMR systems for admitted patients, but lack some administrative data • Health insurers (such as *Salud Total* and *Sura*) have implemented EMR systems that record administrative outcomes • EMRs rarely combine outcomes • There is a project to unify EMR systems for different stakeholders of the healthcare system (*Historia Clínica Electrónica Unificada*)	• Among many objectives, *Mas Salud Occidente* aims to manage the patient interaction with the healthcare network (eg, waiting lists and referrals) • Manages resources such as medical supplies and availability of beds[32,40]
Limitations/challenges	• The sample population at Hospital Italiano may not be widely representative of the Argentinian population because it is a private hospital	• A 2017 study revealed that in a sampled population, only 50% were registered and there were errors including incorrect demographic data[41]	• Lack of information technology infrastructure and connectivity limits integration of the data available from Colombia's healthcare system	• Lack of training and incentives for healthcare professionals to maintain pharmacovigilance systems

Example of national condition-specific database for surveillance and informing health policy: maternal and neonatal databases

	Argentina (Plan Nacer)	Brazil (SisPreNatal)	Colombia (ICBF)	Chile (FONSA and MoH databases)
Summary	• Funding and auditing program to monitor quality and allocation of resources in clinics treating uninsured women and children	• Software developed by DATASUS for collecting follow-up data on>3 million pregnant women in 5000 municipalities in the Unified Health System[31]	• Data freely accessible on the users and resource use of childhood health promotion and disease prevention services, covering early childhood nutrition and programs	• The National Observatory of the Rights of the Child provides databases on key indicators for Chilean children's well-being[51] • The Department of Health Statistics and Information

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Table 1. Continued

Example of national condition-specific database for surveillance and informing health policy: maternal and neonatal databases				
	Argentina (Plan Nacer)	**Brazil (SisPreNatal)**	**Colombia (ICBF)**	**Chile (FONSA and MoH databases)**
	• World Bank and MoH financially incentivize healthcare providers. In exchange, a legally binding agreement between local and national MoH ensures the supply of high-quality data • Systematically monitors performance in different indicators for early detection of pregnancy, obstetric care, prenatal care, immunization coverage, and reproductive health[42] • Argentina is also part of NIHCD's maternal newborn health registry global network, the source of several global studies on maternal and neonatal mortality[43–49]		for families and communities[50] • The SUIN database holds 10 y of data on health, nutrition, education, recreation and sport, and protection for Colombian children at national and municipal levels	also maintains data on birth statistics, birth indicators, and birth charts
Limitations/challenges	• Challenging to reach remote areas and those that do not register for health benefits[42,52]	• As in many information systems, the quality and completion of data are very much dependent on the person in charge of updating the system with the most appropriate information • The huge number of municipalities (>5000) in Brazil poses a limitation in terms of the homogeneity of the data quality and completion recorded in the system	• Reports with lots of tables but only superficial analysis	• High maintenance

DATASUS indicates name of database; EHR, electronic health record; EMR, electronic medical record; FONASA, Fondo Nacional de Salud; HMO, health maintenance organization; ICBF, Institute of Family Welfare; *ICD*, *International Classification of Diseases*; *ICD-10*, *International Classification of Diseases, 10th Revision*; MoH, Ministry of Health; NICHD, National Institute of Child Health and Human Development; REM, Resúmenes Estadísticos Mensuales; REMSAS, Resúmen Estadístico Mensual-Semestral de Actividades de Salud; SIDRA, Information Systems Healthcare Network (*Sistemas de Informacion de la Red Asistencial*); SISA, System of Health Information Systems; SISPRO, Integral Information System of Social Protection; SIVIF, Sistema de Vigilancia Epidemiológica para Violencia Intrafamiliar; SUIN, Unique Child Information System of the National Family Welfare System; SUS, *Sistema Único de Saúde*.

Academics and pharmaceutical industry have advocated for an increased use of RWE, encouraging other potential users to generate the data and use results. In our case studies, we identified some common opportunities to improve the use of RWE:

- The region has witnessed an extension of healthcare coverage in at least 2 dimensions (bigger population and more diseases/interventions covered), which exerts pressure on healthcare budgets. Thus, there is agreement on the need to monitor results closely, particularly those pertaining to high-cost interventions.
- Data registration is improving in all the countries, with various strategies to address specific issues. We have identified initiatives to extend the use of EMRs and improve registration (eg, harmonize coding systems and languages, minimize the use of free text, and train personnel on coding systems) and to improve the traceability of patients and allow for longitudinal follow-up (eg, systems integration and central authorities aiming at extending data consolidation).
- There is a rapidly growing, and maturing, number of HTA units in the MoH and independent HTA agencies in the region.
- There is an increase in the various types of HTA institutions and units in South America, and an increasing adoption of pharmaeconomic guidelines as well as evidence-based healthcare policy design, representing a promising prospect for the extended use of RWE in the region.

Discussion

The literature review indicates that some patient-level data resources exist in the 4 countries under study. Nevertheless, the quality of registries and databases vary and are generally locally managed without standardized coding and practices between disease groups, hospitals, and regions.

The expert contributions reveal that there is occasional use of RWE in HTA submissions, and expertise to analyze the supporting data, but at the time of writing RWE is not consistently

Table 2. Summary of uses of RWE in 4 Latin American countries.

Uses	Argentina	Brazil	Colombia	Chile
Regulatory setting and pharmacovigilance	• Rarely used in marketing authorization decisions • ANMAT manages national pharmacovigilance systems to detect and prevent treatment-related AEs • The ANMAT post-authorization surveillance procedure (provision 8054/10) requires AE and quality data to be collected during commercialization, and any subsequent corrective action to be taken[53] • This enables the early detection of AEs during normal use to ensure real-world safety and effectiveness[53]	• ANVISA executes sanitary control of the production, marketing, and use of products and services subject to health regulation[54] • ANVISA's technovigilance system collects data on AEs and technical complaints related to health products in the post-marketing phase of a product[55] • Before granting authorization, ANVISA requires an economic information report from product developers, including both international and local RWE[56]	• INVIMA (formed under the MoH in 1992) is responsible for inspecting the marketing and manufacturing of health products and implementing health standards and practices for medical approval of import or export products[57] • Regulations are in place to oversee the registration, marketing, and surveillance of production, processing, uses, and maintenance of medical technologies[58]	• The National Centre of Information on Pharmaceuticals and Pharmacovigilance, part of ANAMED, is responsible for the prevention, detection, and research of medicinal product–related AEs[59] • RWE is therefore used to inform ANAMED of a new drug's safety profile postcommercialization • This requires the collaboration of the Institute of Public Health, hospital staff (public and private), and the manufacturers of devices, importers, and patients[60] • Medical product manufacturers are required to ensure medical devices meet safety and effectiveness requirements and maintain data to support this through post–market surveillance[60]
HTA decisions (involving HTA agencies and manufacturers)	• Several official or academic HTAs exist in Argentina (UCEETS, the Institute for Clinical Effectiveness and Health Policy, the HTA Direction within ANMAT, the IMSSET in UBA, and the CETSA in *iSalud*) that have used RWE in their submissions. Nevertheless, these evaluations were not binding until recently • Formal HTAs are required for health technologies that are to be included in the compulsory benefits packages (PMO or SUR) since the MoH resolution of May 2017. This is expected to promote an increase in RWE-based economic evaluations[61] • The pharmaceutical industry has funded a number of cost-effectiveness studies using RWE, albeit limited	• The National HTA agency (CONITEC) was formed in 2011 to define the criteria for HTA submissions to the public health system and to develop clinical guidelines[62] • RWD are frequently used in CONITEC submissions, in particular, epidemiological, resource use, and treatment data sourced from DATASUS[63] • Observational studies, including chart reviews and nonrandomized trials, were used to support decisions, and surveys were used to identify treatment patterns[63] • Between 2011 and 2014, 88.2% of submissions included RWE[14]; most economic models, however, were based on expert opinion and lacked RWE[14] • There is a lack of RWE on national burden of diseases, which impairs appraisal decisions[14] • To submit technologies for reimbursement on the "expensive drugs," producers must submit a dossier including RWE data (as described earlier) to CONITEC[62]	• The Colombian HTA agency (IETS) was established in September 2012 and is responsible for the development and appraisal of evidence-based clinical guidelines, economic evaluations, and budget impact analyses • The IETS is described by the OECD as "one of the most advanced HTA agencies in Latin America" with a transparent and collaborative process of conducting cost-effective analyses[64] • Drug costs data from the 2007 SISMED project, which can be freely accessed online, are used across Latin America in modeling exercises and budget planning[17]	• A 2015 law for funding high-cost drugs prompted the establishment of a comprehensive HTA process[65] • In response, economic modeling is more frequently used, improving the capacity to integrate RWE into HTA submissions[65] • It is expected that the Chilean coverage system will trigger more RWE to be produced and used in HTAs • Economic evidence is currently being produced mostly with international data, although local registries are also used to estimate cost and resource consumption

continued on next page

Table 2. Continued

Uses	Argentina	Brazil	Colombia	Chile
Academic institutions multiple uses	• The IECS, based at the University of Buenos Aires, conducts research on the clinical, economic, and social impact of healthcare drugs, practices, and services • The IECS has a department dedicated to data collection system design, database quality control, and statistical analyses, demonstrating the capability to generate and analyze RWE • Other academic institutions such as the CETSA and the IMSSET conduct research using RWE for scientific dissemination as well	• DECIT-CGATS is a public sector collaboration between the Department of Science and Technology and the MoH. This public organization collaborates with research institutions and public universities to review HTA studies • DECIT-CGATS fosters RWE research by developing monitoring systems for emerging technologies and guidelines to evaluate medical devices[66]	• Government-managed national databases for oral health, mental health, and other disease groups are freely accessible to researchers • A national cancer information system collects data on mortality, incidence, services, and inequality at both local and national levels, but some regions demonstrate undercoverage and there is a lack of peer-reviewed literature on existing data[67] • Researchers are increasingly accessing and analyzing data both from Colombia's compulsory registry Sivigila and the SISPRO information system project[68,69]	• Following the legal boundaries on access to patient data, academic institutions may access RWE only if conducting research that will contribute to the improvement of public health and maintain patient confidentiality[70,71]

AE indicates adverse event; ANAMED, National Drug Regulations Agency; ANMAT, Food, Drug and Health Technology National Agency of Argentina (*Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*); ANVISA, Brazilian National Health Surveillance Agency; CETSA, Center for the Evaluation of Health Technologies; CONITEC, National Committee for Health Technology Incorporation (*Comissao Nacional de Incorporaca de Technologias*); DECIT-CGATS, Coordenação Geral de Avaliação de Tecnologias em Saúde - Departamento de Ciência e Tecnologia; HTA, health technology assessment; IECS, The (Argentinian) Institute for Clinical Effectiveness and Health Policy (*Instituto de Efectividad Clinica y Sanitaria*); IETS, The (Colombian) Agency of Health Technology Assessment (*Instituto de Evaluación Tecnológica en Salud*); IMSSET, Medical Institute for Social Security and Health Technology Assessment; INVIMA, Colombia National Food and Drug Surveillance Institute; MoH, Ministry of Health; OECD, Organisation for Economic Co-operation and Development; PMO, *Plan Medico Obligatorio*; RWD, real-world data; RWE, real-world evidence; SISMED, Sistema de Información de Medicamentos; SISPRO, Integral Information System of Social Protection; SUR, *Sistema Único de Reembolso*; UBA; UCEETS, HTA Coordination Unit of the Ministry of Health (*Unidad Coordinadora de Evaluación y Ejecución de Tecnologías en Salud*).

communicated to HTA agencies at a national level. Local HTA agencies leverage RWE in their decision-making process in the design of clinical practice guidelines, in systematic reviews of efficacy and safety, as inputs in models (both economic and epidemiological), and for resource allocation. The preference for local or international RWE depends on the parameter required to be estimated. If the parameter is likely to be influenced by local practices, such as resource use or an effectiveness estimate, as opposed to an efficacy endpoint, local RWE would be preferred. If the parameter is less likely to be influenced by local practices such as the incidence of a rare adverse event, or durability of treatment response, evidence from a good-quality international source may be admissible, or even preferred. HTAs need to balance the need to foster local RWE without overly delaying the assessments, which are expedited if international RWE is also considered, after addressing transferability issues.

Opportunities lie in increased capacities for regulation and pharmacovigilance in the form of mandatory postauthorization studies or context-specific RWE guidelines. It is also consistently suggested that higher levels of patient involvement may trigger increased levels of safety and effectiveness monitoring.

This research indicates that there are 4 key policy implications to generating RWE and using it to inform decision making. First, a central authority is required to steward health information systems to ensure interoperability and quality guidelines. Second, legal and standard practice frameworks are also needed for data anonymization and linkage that protect patient rights to confidentiality. The Food and Drug Administration does this by sharing only aggregated data beyond local networks, but Colombian regulators, for instance, have not put such a barrier in place, which raises privacy issues. Third, regulation is also required to monitor the transparency and reproducibility of results to ensure viable and mutually beneficial models for collaboration. Finally, the allocation of information technology resources, training, electronic databases, and storage facilities is needed for public healthcare facilities to ensure transferability of routine data collection and patient traceability through the entire continuum of healthcare provision.

There are limitations to this study. Country-specific expert opinion was sought for each case study, resulting in some inconsistencies in the focus and depth of topics evaluated in the countries. Also, since the time of writing (June 2017-January 2018), there may have been updates and changes in the use, laws, or regulations of RWD and RWE. Finally, the pitfalls of comparing South American healthcare systems within the region and to European and American healthcare systems should be highlighted. Although no direct country comparison is possible, the funding mechanisms, epidemiological profile, and basic structure of South American health systems are often fundamentally different from the single-payer systems in Europe or the largely private health insurance–reliant US system. In the region under study, most countries have a mix of private healthcare, social security financing, and public provision for the poor. This means that healthcare is characterized by fragmentation, uneven coverage, and the associated equity issues. Thus, these comparisons should be interpreted with care.

Conclusions

Recommendations for future research are first to monitor and evaluate the uses of RWE produced by the 4 digital initiatives investigated: System of Health Information Systems (Argentina), DATASUS (Brazil), Integral Information System of Social Protection (Colombia), and *Sistemas de Informacion de la Red Asistencial* (Chile). The outcomes of digitalization can be shared with healthcare systems in emerging economies in Latin America and elsewhere, and it is recommended that a regional repository of databases to signpost users to freely available data be set up to facilitate this. Second, it is suggested that future research monitors the uses of RWE in HTA decisions, to pinpoint the regulatory bodies, indications, and populations that include RWE in HTA submissions. Third, the quality of RWD, data analyses, and the resulting RWE is largely unknown. Future research should examine the transferability, reliability, and regional variation in routinely collected healthcare databases as well as the quality of the RWE produced. Finally, future research should monitor the impact of systematically collecting RWD in healthcare settings on patient experience and health outcomes. The results of this study show that a feedback mechanism, such as Argentina's Plan Nacer, can dramatically improve patient care by financing well-run clinics that report high-quality RWD.

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Supplemental Materials

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