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Indicators of Pharmaceutical Supply Chain Assessment in Low and Middle-Income Countries: A Systematic Review of the Literature

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Abstract

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Much of the total global burden of disease is attributable to diseases that are preventable or treatable using modern pharmaceutical drugs. Efficient and effective supply chains are critical to ensuring medicines are available when and where patients that need them, especially in low and middle-income countries where high costs may limit the supply of drugs. Pharmaceutical management has been studied for the past thirty years, but recent global initiatives have brought a surge of attention toward drug supply chains. This attention by a wide variety of parties may have created inconsistency and incoherence in the assessment of pharmaceutical supply chains, thereby limiting comparability and knowledge transfer between contexts. Reported here are the indicators employed by drug supply chain assessments in the peer-reviewed literature. This search included 90 studies in analysis. The most common indicator used was *% drug availability*, however inconsistency in its definition and interpretation limits comparability across studies. Indicators measuring drug procurement and distribution were less commonly used, and were largely unstandardized across studies. The results suggest that pharmaceutical management relies heavily on some indicators, while neglecting to measure other key factors affecting supply chains. Coordinated action and further study are required to address the gaps in the evaluation of pharmaceutical programs.

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Introduction

Many public health interventions depend on the availability, cost, and quality of pharmaceutical drugs. Although an intervention may be designed to meet health needs by delivering a vaccine or medicine to the population, real-world conditions may limit the program's effectiveness if there are pervasive barriers to the selection, financing, manufacturing, distribution, or use of the required drugs. The principal goal of the emerging field of pharmaceutical management is to improve and expand access to quality medicines (Management Sciences for Health, 2012). In low and middle-income countries, this is especially challenging due to a paucity of domestic financial resources, human resources, technical knowledge, political will, or uncoordinated health efforts between public, private, and international actors (Leach, Paluzzi, & Munderi, 2005).

Ensuring access to medicines is critical to improving population health. In 2009, it was estimated that nearly 30,000 children die each day, most of whom die in low and middle income countries from diseases that are preventable or treatable using modern pharmaceutical drugs (World Health Organization, 2009). The United Nations (MDG Gap Task Force, 2012) has also noted that in developing countries, only 51.8% of public facilities and 68.5% of private facilities can provide regular access to essential medicines, which are those specific medicines that "satisfy the priority health care needs of the population" (World Health Organization, 2004a). Nearly twenty percent of global under-five mortality is due to lower respiratory infections. Most of these cases are found in low and middle-income countries, and can be readily cured by administering inexpensive antibiotics (Jamison et al., 2006). Expanded access to medicines has been shown to improve health outcomes. Although HIV/AIDS still kills nearly 1.5 million people each year, enhancing antiretroviral therapy coverage has averted 4.2 million deaths from 1996 through 2012 (World Health Organization, 2013). Diarrhea, a top cause of childhood mortality in developing countries, can be treated at home with oral rehydration salts and

zinc supplements. Ample availability of these seemingly simple medicines has significantly decreased mortality over the past decade (Jamison et al., 2006). There has been some progress towards improving access to medicines, especially after the adoption of the Millennium Development Goals (four of which contain targets directly dependent on pharmaceutical management) (Sarley, Allain, & Akkihal, 2009). However, the WHO (World Health Organization, 2004a) notes that ensuring equity in the administration of medicines is the greatest challenge going forward in pharmaceutical management, and will depend on several key policy directives, including rational selection and use, affordable prices, sustained financing, and reliable supply systems.

To provide some direct focus on pharmaceutical management in low and middle-income countries, Management Sciences for Health a (MSH), a global nongovernmental organization (NGO) that works to improve access and affordability of health services, published the first edition of *Managing Drug Supply* in 1982. The principles that MSH offered in that original text and its follow-up editions have been utilized in various contexts to inform decision making by policymakers, health system managers, health workers, and academic researchers (Management Sciences for Health, 2012). The most recent edition of *Managing Drug Supply*, *MDS-3*, offers a pharmaceutical management framework of four interconnected and overlapping phases: selection, procurement, distribution, and use. Under this framework, a well-functioning pharmaceutical system should be efficient in each of these areas of operation (Management Sciences for Health, 2012).

Selection is the process of deciding which medicines a health system should include in its pharmaceutical strategy to improve access (Management Sciences for Health, 2012). Although the WHO has issued Essential Drugs Lists (EDLs) since 1977 to serve as guidelines, nations are responsible for developing their own lists of essential drugs according to their priorities (Laing, Waning, Gray, Ford, & t Hoen, 2003).

According to the WHO (World Health Organization, 2004b), “Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.” Implicit in this model is that some medicines are more important to population health than other medicines are; therefore, these medicines should be widely available and closely monitored. It has been argued that in the early years of the EDLs, selection was often experience-based rather than evidence-based; however greater professional, academic, and public attention to pharmaceutical management has increased the rigor of selection in many countries (Laing et al., 2003). Smith et al. (Smith & Tickell, 2003) note that amidst evolving trade agreements and international patent laws, using EDLs provides a way to formalize drug selection, thereby prioritizing public health relevance, efficacy, safety, and cost-effectiveness rather than private interests or convenience.

Procurement refers to the process by which a health system acquires the selected medicines. According to MSH(Management Sciences for Health, 2012), “An effective procurement process seeks to ensure the availability of the right medicines in the right quantities, at reasonable prices, and at recognized standards of quality.” As such, procurement includes forecasting required drug quantities, setting production quality standards, choosing suppliers, comparing price quotations, and paying for the drugs. Successful procurement depends on sound business practice while maintaining a priority on improving health outcomes; therefore, the dynamics of the global market for pharmaceuticals and the performance of a health system’s procurement program are interdependent. Use of pooled procurement practices, third-party negotiating organizations, generic medicines, and quality certification programs have decreased costs and opened availability to essential medicines (Burnett, 2003; Ombaka, 2009; Supply Chain Management System, 2009; Waning et al., 2010). However, it has been

shown that for antiretroviral drugs (ARVs) such initiatives decreased the number of buyers and sellers worldwide, decreasing competition. Careful monitoring is required to ensure costs are not driven up in the long term (Waning et al., 2010).

According to the definition in *MDS-3*, the *distribution* element of pharmaceutical management encompasses the logistical handling of medicines and information between the procurers and the health units, as filtered through the varying levels of storage and administration joining procurement with service delivery (Management Sciences for Health, 2012). This definition also includes the information systems used to transfer data to procurers, monitor inventory sizes, and track orders through the supply chain. In the Ivory Coast, technological innovations to the logistical systems improved drug quantification and timely reporting (Supply Chain Management System, 2009). Such logistical and informational functions bridge the mass procurement process with the health unit that uses them.

After the necessary precursory steps of selection, procurement, and distribution, the *use* phase of pharmaceutical management refers to the roles that health providers and patients have in diagnosing, prescribing, educating, dispensing, and adhering to medicine treatment. In developing countries, the primary application of this phase in developing countries is under the principles of rational medicine use. Born from the reality that resources are scarce, *rational medicine use*, when implemented properly, conforms to all of the following criteria (Management Sciences for Health, 2012): 1) prescribing for the appropriate medical indication; 2) prescribing the appropriate medicine; 3) prescribing and delivering the appropriate dosage; 4) prescribing to the appropriate patients, without contraindications or a likelihood of adverse reactions; 5) dispensing medicines correctly, including with sufficient information to patients about the medicine; 6) patients adhering to treatment. A health system that does not engage in rational medicine use may be marked by medicine overuse, polypharmacy, adverse drug

reactions, or patient nonadherence or misunderstanding of instructions (Hogerzeil et al., 1993). Because rational use applies best practices from the fields of medicine, pharmacy, public health, economics, education, and social sciences, interventions to promote rational medicine use require multidisciplinary collaboration. Otherwise, improvements to the other phases of pharmaceutical management may be undermined by decreased rationality (Ross-Degnan et al., 1992).

As a formative component of pharmaceutical management, the supply chain ensures the flow of drugs through the four phases of pharmaceutical management. John Snow, Inc. (JSI) (John Snow Inc, 2012), a well-respected leader in supply chain management, defines a public health supply chain as "a network of interconnected organizations or actors that ensures the availability of health commodities to the people who need them." This characterization is broad because it may refer to personnel and operations at any phase of pharmaceutical management. However, an effective interpretation of the pharmaceutical supply chain generally emphasizes connectivity within the "network of actors" in order to highlight the efficiency of the *flow* of medicines and information through the phases of pharmaceutical management.

Since a full supply chain consists of interconnected yet distinct functions, inaccuracy, inefficiency, or weakness at any point may compromise the strength of the entire supply chain. A disruption anywhere along a pharmaceutical supply chain may ultimately cause a stockout, or unavailability of drugs. Stockouts can cause patients to miss treatments, and may increase risk of mortality if the disruption persists (Ikoh, Udo, Charles, & Charles, 2008; Pasquet et al., 2010). Other intermediate outcomes of poor supply chains include product expiration, theft, overstocking, understocking, order errors, and political/legal blocking (Supply Chain Management System, 2009). It has also been shown in different countries that although a supply chain may be functional at the international and national level, there may still exist a lack of strong supply

management at the local site level, pointing to a need for improved training and investment further down the chain (Kohler & Revathi, 2012; Waako et al., 2009).

In response to the apparent need for supply chain strengthening throughout the global health community, JSI and MSH, who were independently leaders in supply chain consulting, collaborated to launch the Partnership for Supply Chain Management (PFSCM) in 2005. Although it may be argued that concentrated attention on drug supply management dates back to the first edition of *Managing Drug Supply* in 1982 (Management Sciences for Health, 2012), the launch of PFSCM was groundbreaking because it combined the efforts of JSI, MSH, and 14 other organizations, companies, and research institutes for the explicit purpose of advancing and applying the science of public health supply chain management (PEPFAR, 2006). One product of PFSCM was the Supply Chain Management System, a project sponsored by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) to provide support to health systems' supply chains for HIV/AIDS commodities, especially among PEPFAR's focus countries (Supply Chain Management System, 2009). PFSCM has also supported supply chain management among programs that are funded by The Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund) by managing the Voluntary Pooled Procurement Project. This project oversees procurement and distribution for certain health commodities being used in Global Fund programs, which may increase efficiency and lower costs (The Global Fund, 2014).

To further promote the assessment of pharmaceutical supply chains, JSI, MSH, and other organizations have independently developed tools that managers and researchers may employ to assess supply chains (Aronovich, Bieze, Felling, & Chandani, 2006; Management Sciences for Health, 2012; World Health Organization/AIDS Medicines and Diagnostics Service, 2013). These tools vary based on the specific supply chain function they evaluate, the overall purpose of the evaluation, and the drugs carried

in the supply chain. In 2007, the World Health Organization (WHO) began compiling a database of tools available for use in the management of health supply chains. This database has grown to include over 300 tools, with resources available in seven languages (World Health Organization/AIDS Medicines and Diagnostics Service, 2013). Each of these tools provides a set of indicators that decision makers may use to determine the strengths and weaknesses of their health supply chains. Just as the tool employed depends on the purpose and focal point of the assessment, the indicators that are required also depend on the supply chain functions being studied. In addition to the tools it offers, *MDS-3* includes indicators and performance targets that MSH recommends to evaluate pharmaceutical supply chain performance at the different phases throughout the pharmaceutical management process. The indicators generally fall into categories of availability, cost, and quality (Management Sciences for Health, 2012).

Although there has been a surge of attention toward pharmaceutical management and global health supply chains, the quantity and variety of available resources may have created incoherence in the indicators reported in supply chain assessments. Comparability between experiences in pharmaceutical supply chain management across health systems is potentially complicated by both overlap and discrepancy in indicators reported. This may lead to the overutilization of some indicators, and the underutilization of other indicators that have useful applications.

The purpose of this paper is to systematically review the evidence to determine the indicators of availability and cost in the procurement and distribution phases that have been employed in pharmaceutical supply chain assessments in low and middle-income countries. Indicators of availability and cost were selected as the focus of this review because they provide a robust determination of the overall performance of a pharmaceutical supply chain. Indicators of quality were excluded from this review

because such indicators focus on drug efficacy and safety and not on pharmaceutical access. The information from this review will help clarify and contextualize the numerous methods of pharmaceutical supply chain assessment, thereby facilitating the sharing of experiences and revealing the strengths and gaps of modern pharmaceutical supply chain assessment.

Methods

Search Procedure

A search was conducted to compile assessments of pharmaceutical supply chains that have been published in the peer-reviewed literature. Three databases of academic references were used to conduct initial searches: PubMed, Web of Science, and Google Scholar. Search terms used are listed in **Appendix A**. The literature search also relied heavily on "snowball" methods, as cited references and database-generated similar articles were also reviewed for relevance. The years of publication for each search were limited to retrieve articles published between 2005 through 2013. This start date corresponds with the recent escalation in attention, research, and funding for public health supply chain management, as marked by the launch of PFSCM (PEPFAR, 2006; Supply Chain Management System, 2013). Only articles available in the English language were reviewed.

Inclusion/Exclusion Criteria

All studies were compared to pre-established criteria for inclusion in the review. These inclusion criteria are outlined in **Table 1** below. Supply assessments for a single drug or a single disease do not necessarily reflect the strength of the health system supply chain; nonetheless, these studies were included in this review because the

indicators utilized may be practically useful to employ in broader contexts. Studies that exclusively referred to the pharmaceutical supply management phases of selection or use were excluded from this review. Although drug selection and use have been evaluated in literature (Ross-Degnan et al., 1992; Smith & Tickell, 2003), the performance of these two phases tends to reflect factors outside of supply chain performance (e.g. politics, patient characteristics, and health provider knowledge). Studies utilizing only indicators of drug quality and drug affordability were also excluded, because these indicators do not necessarily reflect supply chain performance; rather, they measure medical efficacy of drugs and patient characteristics, respectively. There was no requirement regarding the presence or type of comparison used. The choice of comparator depends on the purpose of the study, but is not necessarily indicative of the methodological strength of a supply assessment.

Table 1. Population, Intervention, Comparator, & Outcome (PICO) Table for Inclusion and Exclusion Criteria

Population	All low to middle-income countries, as defined by The World Bank (The World Bank, 2014)
Intervention	Any quantitative supply chain assessment for any combination of pharmaceutical drugs, if the assessment determines performance of at least one of the following supply chain functions (Management Sciences for Health, 2012): 1) the overall supply chain; 2) the procurement phase (including forecasting and purchasing); or 3) the distribution phase (including central storage, transportation, and health unit storage) Excludes: qualitative studies, supply assessments of non-drug health commodities, studies examining drug selection to essential/core medicine lists, studies solely determining medicine use, studies of medical effectiveness of drugs
Comparator	No requirement
Outcome	1) Any quantitative indicators of drug *availability* 2) Any quantitative indicators of *cost* that are attributable to included supply chain phases Excludes: qualitative findings, indicators of drug selection to essential/core medicines lists, indicators of prescribing/distribution practices at health units, indicators of patient affordability of drugs, indicators of retail drug price without any price component or markup analysis, indicators of drug quality

Data Abstraction/Analysis

Articles meeting the criteria above were compiled into an abstraction table using Microsoft Excel. For each included study, the spreadsheet noted the author, study timeline, methods used, geographic location, comparison characteristics, supply management phase assessed, and all relevant availability and cost indicators.

This review depends on the indicators employed by the included studies, rather than on the values and results reported by the studies; therefore, this review used no meta-analysis or grading of methodological rigor. Studies with different purposes, metrics, and outcomes should not be compared according the same criteria (Guyatt et al., 2011). However, the data source used to populate an indicator affects that indicator's reliability and usefulness for monitoring. Therefore, the use of secondary data was examined in each supply phase in order to determine data collection methods used to populate the indicators used in pharmaceutical supply chain assessment. Studies were designated as using secondary data if they explicitly noted use of data that was initially collected, analyzed, and reported by a party apart from the investigators. Sources of secondary data were preexisting datasets, data libraries, evaluations, or organizational reports; while primary data sources included interviews, focus groups, observations, and surveys. The associations between the use of secondary data and the supply phase assessed were estimated using odds ratios ($p<0.05$) and proportions, calculated using Microsoft Excel and tables generated in EpiInfo 7.

Results

The literature search produced 101 articles that are relevant to the research question. Of these, 11 were excluded for being editorials, commentaries, or articles otherwise lacking a quantitative research component. This produced a sample of 90

studies that were included in analysis. The full citations of included studies are listed in **Appendix B**. There were 11 studies that assessed pharmaceutical supply chains in more than one world region, as defined by the World Bank (The World Bank, 2014). The number of studies from each world region is shown in **Table 2**, along with the percentage of total studies that include an assessment of each region. A majority of studies (47 studies, 52.2%) provided supply assessments of programs in Sub-Saharan Africa. The Middle East & North Africa had the fewest assessments published (12 studies, 13.3%).

Table 2. World Regions of Pharmaceutical Supply Chain Studies[a]

World Region	# of studies[b] (n)	% of studies (n/90*100)
East Asia/Pacific	26	28.9
Latin America	24	26.7
Middle East/N Africa	12	13.3
South Asia	23	25.6
Sub-Saharan Africa	47	52.2

[a] World Region as defined by World Bank, 2014.
[b] 11 of 90 studies encompassed more than one World Region. Values do not sum to total number of included studies

The purpose of each included study was reviewed in order to categorize the assessments by the geographic scope analyzed. The frequencies of assessments at each geographic level- international, national, regional, and site- are shown in **Table 3** (next page). When combined, a large majority of studies were focused at either the national or regional levels (33.3% and 43.3% respectively), whereas fewer studies evaluated pharmaceutical supply at the international and site levels (16.7% and 6.7% respectively). There were only 6 studies that were focused at the site level.

Table 3. Geographic Scope Assessed by Pharmaceutical Supply Chain Studies

Geographic Level	# of studies (n)	% of studies (n/90*100)
International	15	16.7
National	30	33.3
Regional	39	43.3
Site	6	6.7
Total	90	100

The frequency of studies evaluating each phase of pharmaceutical supply management was varied. As shown in **Table 4** (below) , 78.9% of the studies assessed the overall supply chains, whereas the procurement (42.2%) and distribution (47.8%) phases were each included in a minority of studies. There were 48 studies which assessed more than one of the phases of supply management relevant to this review.

Table 4. Pharmaceutical Supply Phases Assessed by Studies

Supply Phase	# of studies[a] (n)	% of studies (n/90*100)
Overall	71	78.89
Procurement	38	42.22
Distribution	43	47.78
[a]48 of 90 studies assessed more than one Supply Phase. Values do not sum to total number of included studies		

Methods used by the studies varied and were often mixed or unclear. The use of secondary data analysis, collected from other studies, government documents, or program reports, was positively associated with assessment of the procurement phase of drug supply management (OR= 9.51; p<.001). Assessment of the overall supply chain or the distribution phase were negatively associated and unassociated with use of secondary data, respectively. **Table 5** (next page) shows the effect of choice of supply phase assessed on the use of secondary data.

Table 5. Association between Supply Phase Assessed and Use of Secondary Data[a]

Supply Phase Assessed	Proportion (# studies using secondary data/# studies of phase)	Odds Ratio (95% CI)[b]	p-value[c]
Overall	21/69	0.05 (0.01, 0.22)	<0.001
Procurement	27/37	9.51 (3.62,26.7)	<0.001
Distribution	16/42	0.67 (0.28, 1.59)	0.18

[a] 2 of the 90 included studies were omitted due to unclear data collection methods
[b] Conditional Maximum Likelihood Estimate of Odds Ratio used due to small sample sizes
[c] Mid-P exact p-value used due to small sample sizes

The review identified 73 unique indicators to assess the three phases of pharmaceutical supply chain management. Indicators were expressed as a percentage (%), empirical number (#), cost ($), or time. For the purposes of this review, different formulations of the same indicator were generally combined into one indicator (e.g., median stockout duration, mean stockout duration, and stockout duration per site were combined into one indicator: *stockout duration*).

Indicators of Overall Supply Chain

According to the guidelines presented in *MDS-3* (Management Sciences for Health, 2012), the 12 indicators used to assess the overall supply chain (**Table 6.** next page) were mostly outcome indicators because ensuring availability of drugs to patients is the principal purpose of a pharmaceutical supply chain. That is, these indicators addressed drug availability at the dispersal sites without examining the processes of the supply chain or the other variables affecting it, as is the case in an assessment of site level geographic scope. The most commonly reported indicator among all phases of supply management was *% availability*; however, this indicator was generally poorly and inconsistently interpreted in the literature. Two common methods of calculating *% availability* are "per site," where the number of available drugs is determined as a fraction of the total number of sampled drugs, and "per drug," where the number of sites

with a specific drug available is determined as a fraction of the total number of sites assessed. These two definitions were left combined as one indicator in Table 6 for two reasons: 1) there is consistently poor specification of methods and interpretation of results in the literature, and 2) the resulting value will be the equal at the aggregate, as long as the full basket of drugs are evaluated for availability at the full sample of sites. The implications of these interpretation issues are discussed in detail in the following section.

Table 6. List of Indicators for Overall Supply Chain, in order of frequency of use

Availability Indicators	# of Studies
% availability	55
% sites with stockout	10
% availability of ANY drug	9
stockout duration	6
# drugs with stockout	3
% time drug available	2
% patients reporting stockout	2
# provider complaints about supply system	2
% sites with stockout of ALL drugs	2
# product-days of stockout	1
stockout duration of ALL drugs	1
# levels of supply chain	1

Most of the remaining indicators for overall supply chain function measure stockout, or unavailability of drugs. The indicator *% availability of ANY drug* is a measure of stockout risk in practical application since it only requires 1 drug of a specific type to be present. This indicator was used in 9 studies, all of which assessed the supply of treatment for a specific disease group (e.g. antimalarial drugs). The indicator *# levels of the supply chain* was a process indicator reported in only 1 study; however, it applies to the functionality of the overall supply chain since it requires the identification of all of the distinct operations at work throughout the supply chain.

Indicators of Procurement

There were 34 unique indicators for procurement, all of which were input indicators due to the nature of this phase of supply management. Of these procurement indicators, 17 were indicators of pharmaceutical availability and 17 were indicators of pharmaceutical cost. These indicators, along with the number of studies using each, are listed in **Table 7**.

Table 7. List of Indicators for Procurement, in order of frequency of use

Availability Indicators	**# of Studies**	**Cost Indicators**	**# of Studies**
# drugs procured total	3	*Median Price Ratio (MPR) at procurement*	15
# manufacturers	3	*$ expenditures total*	7
# generic brands available per drug	3	*$ expenditures per unit*	4
# drug doses procured	2	*$ expenditures per patient-year*	4
# importers	2	*% drugs with higher (or lower) cost than comparison*	3
% drugs from domestic manufacturers	2	*$ saved*	2
# orders made	2	*# drugs higher (or lower) cost than International Reference Price (IRP)*	2
% response rate of sites to stock level request	1	*% of $ procurement expenditures to generics*	2
time for sites to respond to stock level requests	1	*% companies with prices approved by a monitoring agency*	1
# drugs requested	1	*MPR after cost and freight*	1
% drugs requested that were not procured	1	*$ equivalent of total donated drugs*	1
% licensed drugs that are produced	1	*% of $ allocated to procurement actually spent*	1
# licenses held per manufacturer	1	*% difference between negotiated price and price paid*	1
% difference in # patients (after procurement change)	1	*% Gross National Product (GNP) spent on public drug procurement*	1
# boxes of drugs ordered	1	*# manufacturers providing quotations*	1
% drugs procured by a procurer	1	*% of $ procurement expenditures used on each drug (or disease)*	1
% total market share procured from a supplier	1	*$ expenditures per Defined Daily Dose*	1

The most commonly used indicator to assess the procurement phase was the *Median Price Ratio (MPR)*. This indicator compares the procurement price per unit of a drug to a global price norm. Since price norms, or International Reference Prices (IRP), are standardized by MSH, the definitions and interpretations of this indicator were consistent across the literature. Total pharmaceutical procurement costs (*$ expenditures total*) was the second most common indicator, being referenced in 7 studies. Availability indicators of procurement were much less commonly shared. The most common indicators, *# drugs procured total*, *# manufacturers*, and *# generic brands available per drug* were each only used in 3 studies.

Indicators of Distribution

The literature provided 27 indicators of distribution, as shown in **Table 8** (next page). The majority, 21, of these indicators were indicators of availability. The remaining 6 were indicators of cost. All distribution indicators were process or output level indicators.

Because the distribution phase includes all levels of storage and transportation, there are a variety of types of indicators that may be employed to evaluate drug availability and cost. The most common availability indicator, utilized in 9 studies, is *% availability among stores*. This was the same indicator as that which was used to measure the overall effectiveness of the supply chain; however, in this phase *% availability* relates specifically to storage centers at the international, central, or district level rather than at drug dispersal sites. Since the definition and interpretation was the same, in the literature it was subject to the same flaws as *% availability at the site level*. Measuring waste, usually defined as theft or expiry of drugs, was also of priority in 5 studies. Output indicators of operational procedures and transport speed were also included, although in fewer frequencies. Cost indicators in the distribution phase mostly

relate to markups. Where there was a price corresponding to at least one intermediate phase of the supply chain, studies reported *% markup per phase of distribution*. Otherwise, supply chain assessments reported the *total % markup* from procurement to retail.

Table 8. List of Indicators for Distribution, in order of frequency of use

Availability Indicators	**# of Studies**	**Cost Indicators**	**# of Studies**
% availability (among stores)	9	*% markup per phase of distribution*	9
% drugs wasted	5	*% markup total (procurement to retail)*	7
% sites with staff trained in stock management	4	*% change in retail price (after supply intervention)*	1
lead time	3	*$ wholesale price*	1
% sites with supply chain operating procedures	3	*% contribution of each phase markup to final retail price*	1
% sites with pharmacist	3	*# distributors providing price quotations*	1
stock size	2		
% sites with standardized records	2		
% drugs properly labelled	2		
% records corresponding to observed stock	2		
# suppliers per site	2		
% sites with drug tracking system	2		
% of transport via mode of transportation (car, bike, foot, etc.)	1		
% drugs available at store that are available on site	1		
time required by providers to distribute medicines	1		
% attrition among distributors	1		
# sites with insufficient quantity of requested drug	1		
% change in # sites	1		
% of ordered drugs that are now available on site	1		
# drugs stocked by only 1 wholesaler	1		
% sites able to order requested drug	1		

Discussion

This review assumes that the published literature accurately reflects the actual usage of pharmaceutical supply chain assessment for decision making within a health system. Since the indicators included in analysis are used more commonly for monitoring than for evaluation, managers may not publish their data in the literature; therefore, this initial assumption may not be valid. Program and supply chain managers generally publish in non peer-reviewed literature or program documents. Although this is appropriate for a primary audience of managers, it also limits the public availability of comparative studies. Nonetheless, the inclusion of 90 studies in the analysis suggests that there has been significant study of pharmaceutical supply chains since 2005. Based on this review, it cannot be concluded that PFSCM definitively drove the study of pharmaceutical supply chains, because this review's included supply chain assessments were most commonly for antimalarials (17 studies) and Essential Medicines of multiple disease categories (29 studies). Nonetheless, the sheer number of assessments published shows that there is an established need and, subsequently, an emerging response for public health supply chain strengthening in developing contexts. In particular, the high percentage of the total studies focusing in Sub-Saharan Africa (**Table 2**) likely reflects a greater need for pharmaceutical supply assessment in the region. Sub-Saharan Africa carries an especially high burden of diseases that are preventable with modern drugs (World Health Organization, 2009). Since the region also consists almost entirely of low and middle-income nations (The World Bank, 2014), the use of indicators of availability and cost are especially important in drug supply monitoring to ensure resources are used as cost-effectively as possible. Although the Middle East/North Africa region also contains several low and middle-income nations (The World Bank, 2014), the relatively sparse number of studies focused there may be due to a combination of factors. The low

proportion of studies may be indicative of national and international inability or failure to emphasize pharmaceutical management in the region. The region's instability caused by war may support this notion, especially in Syria and its bordering nations. Much of the public health work has been done by international NGOs, who may not experience the same supply issues faced by a government-run health system. Even if operated by external organizations, efficiently managed supply chains will not be featured in published literature as commonly as supply chains that are less effective. On the other hand, drug supply systems may not be understudied; rather, the primary problems faced in the region may require concentration on indicators that were excluded from this review, such as indicators of quality, selection, or rational drug use. Further study is needed to determine the effectiveness of pharmaceutical supply systems and their assessments in the Middle East/North Africa region.

Similarly, the frequencies of included studies that assessed supply chain performance at the different geographic scopes reveal potential gaps in the current application of drug supply assessment (**Table 3**). Since over two-thirds of the studies examined supply chains at the national and regional level, this suggests that the majority of pharmaceutical supply monitoring and decision making occurs at these levels. Comparably little data appear to be utilized specifically for international or site use. Only 6 studies analyzed drug supply at the site level, which may be indicative of a dearth of drug supply management at the site level. Waako et. al. (Waako et al., 2009) have found that even among nurses and pharmacy assistants, capacity to properly manage drug supply is weak at local clinics. A study of ARV supply chains has also found that operations are most often compromised at the site level, causing the greatest percentage of total product losses (Kohler & Revathi, 2012). Primary data collection for regional and national assessments necessitates site level data collection and analysis with the intent of aggregating the data. However, employing performance indicators specifically for site

level analysis and use may inform and improve site level pharmaceutical management, thereby improving supply chain performance overall.

The frequencies of indicators utilized in the literature show that some applications of pharmaceutical supply management are popular in literature, while other applications are neglected. The percentage of studies that assess each drug supply chain phase is useful to ascertain how often each phase's indicators are used (**Table 4**). Over half of the included studies utilized indicators of more than one supply chain phase. Since the phase assessed depends on the specific purpose and audience of the study, examining multiple supply phases suggests that assessments are often undertaken with more than one narrow purpose. While broad scopes of work may complicate analysis and interpretation of the results, utilizing indicators of multiple drug supply phases may also allow for a more comprehensive assessment of the functionality of each phase of the supply chain. Similarly, the large percentage of studies that utilized indicators of the overall supply chain may not necessarily be indicative of inadequate assessment of the other phases. Since the majority of indicators for the overall supply chain are the outcome indicators of pharmaceutical availability, these should be included in most supply chain assessments.

Despite the frequent use of overall supply chain indicators as a category, attention toward these indicators is narrowly fixated around *% availability*, which constitutes the majority of all indicator use within this phase (**Table 6**). As one of the most fundamental indicators highlighted in *MDS-3* (Management Sciences for Health, 2012), this indicator's wide use in the literature reflects its practical application for decision making. The other indicators reported less frequently provide additional information that should be more commonly considered in literature. In particular, indicators of drug supply duration (i.e. *stockout duration*, *% time drug available*, *# product-days of stockout*, and *stockout duration of ALL drugs*) provide necessary data

on how often drugs are available over a time period. Although they require longer or more detailed data collection- likely explaining their underuse- these indicators provide useful information not captured in the more popular indicators, which generally focus on the total unavailability of drugs or the availability of just 1 dose on a single day. That is, indicators of *% availability* or *% stockout* rely on the data collected from a single visit or day of survey (Management Sciences for Health, 2012), thereby limiting their interpretation if used as a sole method of data reporting.

Inconsistency and ambiguity in the methodology used to acquire an indicator of *% availability* also limits both the interpretation of data within studies and comparability of data between studies. As previously mentioned, this indicator may be populated and interpreted using two distinct methods. Although the resulting values may be equivalent between the two methods, the lack of consistency makes it less useful in practical supply chain management. In order for a manager to properly diagnose an issue in the supply chain, he/she must be able to ascertain whether the problem is with certain drugs or at certain sites. Taken alone, *% availability* does not facilitate that determination. Further inconsistency in *% availability* is due to the varying "case definitions" of what constitutes availability, and how it is verified. One recent study (Choi & Ametepi, 2013) noted four possible definitions of *% availability* that are currently in use in different contexts of drug supply management:

1) % observed availability of at least 1 unexpired dose (the reference definition),

2) % reported availability of at least 1 dose,

3) % observed availability of at least 1 dose, regardless of expiration,

4) % observed availability with all doses unexpired.

These definitions represent varying degrees of rigor, and yield different results depending on which definition/method is employed (Choi & Ametepi, 2013).

As a whole, the indicators of procurement provide a comprehensive measure of the effectiveness of that phase (**Table 7**). Because there are several distinct processes to monitor in procurement, the indicators vary in order to track the actors involved, expenditures used, and drugs procured. While the robust breadth of procurement indicators is helpful to managers seeking to assess their procurement process in multiple ways, there is also a lack of coherence between studies. Only 2 indicators, *MPR* and *$ expenditures*, have been used in more than 5 studies; therefore, only these cost indicators have emerged as standard measures of procurement effectiveness. Unlike *% availability* in the assessment of the overall supply chain, *MPR* seems to be consistently and clearly defined. This may be because the International Reference Prices that determine *MPR* are standardized and regularly updated by MSH (Management Sciences for Health, 2012), making it resistant to misinterpretation. Recent efforts by PFSCM, Global Fund, WHO, and others have specifically targeted the procurement of pharmaceutical drugs to open and pool procurement processes, leading to the public sharing of MPRs and expenditures. The primary objective of such initiatives is to decrease procurement costs; therefore cost indicators may be highlighted in the literature to maintain this focus on cost (Supply Chain Management System, 2009; The Global Fund, 2014; World Health Organization/AIDS Medicines and Diagnostics Service, 2013).

Since this review revealed that procurement indicators of availability are not as commonly studied or shared, this suggests they may have less relevance from a management perspective. Since procurement is concerned with the quantification and purchasing of drugs, it may be argued that much of the relevant information that is obtained using the availability indicators of procurement can also be captured using a combination of cost indicators of procurement and overall availability indicators. These two categories of indicators, when combined with measures of drug affordability, have

been utilized to infer the general effectiveness of pharmaceutical programs in India (Kotwani, 2009, 2013; Kotwani et al., 2007). However, availability indicators of procurement are still essential to pharmaceutical management because they may identify factors affecting the quantity and movement of drugs as they enter the supply chain. These indicators require greater attention in the literature.

It is important to note that among the included studies in this review, only those addressing the procurement phase were significantly associated with the use of secondary data (**Table 5**). This is likely because procurement is mostly performed in bulk at a national and international level, and primary data on cost and availability is difficult to collect at those levels. However, in economic research- which may contribute to procurement assessment, depending on the indicators employed- it has been noted (Atkinson & Brandolini, 2001) that dependency on secondary data potentially limits methodological integrity. That is, results of studies using secondary data may be biased due to failure to identify inconsistency in primary data collection methods, improper adjustment of key statistics, or misinterpretation of study characteristics. Indicators of procurement currently rely on secondary data, so these indicators may be susceptible to similar biases. Further study is required to ascertain the extent to which these indicators are reliable. Additional indicators and/or data collection methods for the procurement phase should also be considered if data integrity is found to be threatened.

Similarly to the procurement phase, the variety of functions and actors involved in pharmaceutical distribution require a wide array of indicators to monitor the entire phase (**Table 8**). Rather than focusing directly on % *availability*, many of these indicators measure other variables in the supply chain that may affect drug supply availability and management. Since these indicators are process and output indicators, practical application is especially important in the choice of indicators to employ, particularly the ability of the indicator to pinpoint a strength or weakness in the

distribution chain. Drug supply monitoring depends on the ability to isolate specific weaknesses in the management of drugs once they enter the supply chain during procurement. Therefore, the low usage of availability indicators in literature could reflect a lack of detail in modern supply chain assessment, a lack of dissemination of these key findings, or lack of consistency and standardization in the indicators applied to distribution. Only *% availability among stores* was reported in more than 5 studies. Expanded usage, dissemination, and consistency of availability indicators for drug transport, central/regional storage, and site level management capacity will improve the body of evidence on pharmaceutical supply chain performance by facilitating the study and comparison of processes and outputs, not just overall availability outcomes.

The principal application of cost indicators in the distribution phase is the analysis of markups, or the added cost applied to drugs after they are initially procured for shipping, fees, and handling. Although *% markup total* is useful as an initial determination of how efficient the distribution process is overall, it does not facilitate the detailed analysis that *% markup per phase* does. The additional data provided by reporting costs at each phase of distribution improves the potential application of the analysis for targeted decision-making and distribution strengthening.

Conclusion

The body of literature assessing pharmaceutical supply chains in developing countries appears to be substantial. However, considering the variety of functions and objectives involved in a full pharmaceutical supply chain, the indicators utilized in these assessments significantly lack variability, consistency, and practical applicability. Specifically, academic researchers, health system and organizational officials, and

reviewers of scholarly publications should devote coordinated action and academic study the following priorities from the evidence:

1. The inconsistency of definitions and methodology applied to *% availability*
2. The reliance on *% availability* as the primary indicator of overall supply effectiveness
3. The lack of pharmaceutical supply assessment in the Middle East/North Africa Region
4. The lack of use of availability indicators of procurement
5. The lack of use of all indicators of distribution
6. The lack of a standardized set of availability indicators of distribution
7. The lack of primary data use in procurement assessment

To decrease the global burden of preventable and treatable diseases, pharmaceutical supply chains must be monitored and managed in a way that will ensure the proper medicines are available when and where patients need them.

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Appendix A

Summary of Search Terms Used to Identify Relevant Literature

Database	Search Terms
PubMed	1. ("Drugs, Essential/supply and distribution"[MAJR]) 2. (("Pharmaceutical Preparations/economics"[Mesh] AND (("supply and distribution"[Subheading] OR ("supply"[All Fields] AND "distribution"[All Fields]) OR "supply and distribution"[All Fields] OR "supply"[All Fields]) AND chain[All Fields])) OR ("Pharmaceutical Preparations/supply and distribution"[Mesh] AND cost[All Fields])) OR ("Pharmaceutical Preparations/supply and distribution"[Mesh] AND availability[All Fields]) OR ("Pharmaceutical Preparations/supply and distribution"[Mesh] AND stock[All Fields]) 3. ("Drugs, Essential/economics"[Mesh] OR "Drugs, Essential/organization and administration"[Mesh] OR "Drugs, Essential/statistics and numerical data"[Mesh] OR "Drugs, Essential/supply and distribution"[Mesh]) 4. ("Pharmacologic Actions/supply and distribution"[Majr] AND availability) OR ("Pharmacologic Actions/supply and distribution"[Majr] AND cost) OR ("Pharmacologic Actions/supply and distribution"[Majr] AND procurement) OR ("Pharmacologic Actions/supply and distribution"[Majr] AND storage)
Web of Science and Google Scholar	Pharmaceutical OR Drug OR Medicine OR "Essential Medicines" OR "Core Medicines" AND Supply OR Distribution OR Procurement OR Storage OR Delivery OR Transportation OR Availability OR Quantity OR Cost OR Price NOT Illicit OR Illegal OR Counterfeit OR "Street Drugs"

Appendix B

Full citation list of articles included in review

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