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Fixed dose drug combinations – are they pharmacoeconomically sound? Findings and implications especially for lower- and middle-income countries

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PERSPECTIVE

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Fixed dose drug combinations – are they pharmacoeconomically sound? Findings and implications especially for lower- and middle-income countries

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ABSTRACT

Introduction: There are positive aspects regarding the prescribing of fixed dose combinations (FDCs) versus prescribing the medicines separately. However, these have to be balanced against concerns including increased costs and their irrationality in some cases. Consequently, there is a need to review their value among lower- and middle-income countries (LMICs) which have the greatest prevalence of both infectious and noninfectious diseases and issues of affordability.

Areas covered: Review of potential advantages, disadvantages, cost-effectiveness, and availability of FDCs in high priority disease areas in LMICs and possible initiatives to enhance the prescribing of valued FDCs and limit their use where there are concerns with their value.

Expert commentary: FDCs are valued across LMICs. Advantages include potentially improved response rates, reduced adverse reactions, increased adherence rates, and reduced costs. Concerns include increased chances of drug:drug interactions, reduced effectiveness, potential for imprecise diagnoses and higher unjustified prices. Overall certain FDCs including those for malaria, tuberculosis, and hypertension are valued and listed in the country's essential medicine lists, with initiatives needed to enhance their prescribing where currently low prescribing rates. Proposed initiatives include robust clinical and economic data to address the current paucity of pharmacoeconomic data. Irrational FDCs persists in some countries which are being addressed.

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Fixed dose combinations; pharmacoeconomics; adherence; medicines; non-communicable diseases; infectious diseases; lower and middle income countries

1. Introduction

Fixed dose combinations (FDCs) are defined as a combination of two or more active ingredients within a single form of pharmaceutical administration [1–6]. They have been shown to appreciably reduce the risk of medication non-adherence, which is particularly important in patients with chronic diseases [7]. However, their rationality for use should be based on sound medical principles as there have been concerns with their irrationality and utility in several countries [1,2,4,5,8].

We will present concerns in more detail in Section 1.1. However, these concerns have to be balanced against the potential advantages of FDCs including their cost-effectiveness in certain situations. These advantages will be discussed in detail in Section 1.2 before debating potential ways forward to enhance the prescribing and funding of valued FDCs. Alongside this, limit authorization, utilization, and funding for medically irrational FDCs and/or FDCs of perceived limited value.

Article Highlights

- Fixed dose combinations (FDCs) are welcomed across countries illustrated by endorsement from the World Health Organisation
- However there are concerns including their rationality, potential to increase adverse drug reactions, dosing schedules with peak effectiveness at different times, lack of titration and potentially higher prices
- There is a paucity of data among low- and middle-income countries assessing their value and cost-effectiveness in routine clinical care affecting availability and funding
- Perceived benefits regarding FDCs among senior-level personnel working in LMICs include simplifying the treatment schedule – especially important in complex disease areas, improved adherence rates and tolerability, reduced overall costs and reduced chances of stock-outs
- Additional perceived concerns include the potential for overtreatment if physicians and patients are not fully aware of their constituents, potential to increase polypharmacy and missed doses have a greater impact on subsequent patient care
- Initiatives to enhance the prescribing and dispensing of FDCs where valued include physician and patient education, developing quality indicators around their use, accelerating their registration and companies having realistic pricing expectations
- Possible initiatives to reduce or negate the availability of FDCs where there are concerns include a requirement for companies seeking registration to provide robust health technology assessment data to support the application as well as improved physician education and greater interaction with national patient organisations

1.1. General concerns with FDCs especially among lower- and middle-income countries (LMICs)

Concerns with FDCs include potentially altering the optimal dosing of one or more of the components due to differences in pharmacokinetic profiles and half-lives of the various constituents [1]. FDCs may also increase the chances of adverse drug reactions or drug:drug interactions due to the different profiles of the medicines in the FDC as well as not fully recognizing the differences that can occur in the pharmacogenetic profiles of patients during the development of FDCs [1,6,9,10]. Pharmacogenetic concerns are particularly important in FDCs when the components are either an essential part of the primary pathway for eliminating the medicines of interest or a critical step in their onset of action [6]. The pharmacokinetic profiles of the constituents in FDCs are also important in patients with infectious diseases as there can be concerns with resistance development due to the combination [11,12]. Additionally, pharmacokinetic and pharmacodynamic considerations of the constituents are important in the elderly where safety profiles may be altered [13]. Evidence has also shown that inappropriately manufactured FDCs can result in their reduced effectiveness or enhanced toxicity in routine clinical care as well as peak effectiveness at different times alongside concerns with their shelf life [14].

Additional concerns with FDCs include potentially higher prices than the sum of the individual components unless justified, higher prices maintained with additional patent protection, difficulty in ascertaining which component is responsible for any side-effects that may arise, and patients may receive too little or too much of a specific ingredient due to challenges with dose adjustments. Besides this, FDCs can encourage an imprecise diagnosis especially for patients with infections and there can be a loss of effectiveness if patients forget to take their FDC as opposed to just one of the individual components [1,5,6,15–18]. There are futhermore concerns that FDCs may become too large impeding oral administration [13,19].

However, some of the perceived difficulties and concerns with FDCs can potentially be addressed through having multiple formulations available for titration purposes, starting FDCs only when deemed safe to do so, and/or addressing pharmacogenetic and pharmacokinetic concerns during FDC development [5,6,20,21]. Alongside this, look to re-formulate large FDCs with dissolving and other formulations [13,22]. The availability of multiple formulations was particularly important for FDCs containing inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs) for treating patients with asthma when health authorities, particularly among Western countries, were looking to reduce the doses of steroids in the ICS/LABA FDCs for long-term safety reasons [23]. The lack of different formulations of ICS/LABA FDCs among the pharmaceutical companies promoting cheaper alternatives reduced their uptake initially until this was addressed [23].

A number of these concerns led to the discontinuation of more than 90% of the FDCs marketed in the US in the 1960s and 1970s [5,24]. Following this, the US Food and Drug Administration (FDA) declared that any new FDC required proof of benefits versus the single components before approval, with similar initiatives in Europe [15,24]. In Europe, the revised regulations from the European Medicines Agency (EMA) stated that any proposed FDC should be based on robust and valid therapeutic principles with the potential advantages assessed in studies against potential disadvantages, and where possible for each dose of the medicines included in the FDC [5,15,25]. Typically, the medicines in FDCs should have different mechanisms of action but their pharmacokinetics and/or pharmacodynamics should not be appreciably different as this will impact on their effectiveness in clinical care. In addition, the combination should not be additive in terms of increased toxicity [1,5,25]. Following these regulatory changes, we have seen a growth in the number of FDCs available across countries. For instance, in Europe using 2009 as a baseline, there has been an 8% increase in FDCs approved by EMA in 2011 and a 15% increase in 2013, with this trend continuing [5].

Stringent control measures are typically needed to reduce the availability of irrational FDCs, which has not always been the case [1,14,26,27]. In India, irrational FDCs were often made available by state authorities without prior approval of the Central Drugs Standard Control Organization [28]. However, these concerns have now been recognized resulting in a recent ban on 328 FDCs in India [29]. Whilst there have been concerns with the quality of generic medicines in Pakistan, there appeared to be no concerns with the bioavailability of for instance rifampicin in FDCs in Pakistan to treat patients with tuberculosis (TB) [30,31].

1.2. Potential advantages of FDCs

Potential advantages for FDCs compared with prescribing the components separately or where there are concerns with monotherapy alone include: (i) improved response rates where there is an inadequate response to monotherapy through for instance different mechanisms of action of the medicines in the combination, (ii) the combination of the medicines in the FDC achieves the desired effect more rapidly, (iii) the proposed FDC reduces toxicity with one medicine potentially counteracting the adverse reactions of another and (iv) the potential for combining doses that are subtherapeutic when used as monotherapy because of issues such as safety as seen for instance with combination medicines for patients infected with human immunodeficiency virus (HIV), with these benefits often translating into lower costs of care [3,15,25,32–36].

FDCs also offer the possibility to simplify administration where a combination of active substances is already recognized as clinically important. As a result, seeking to improve adherence as well as targeting multiple disease pathways, improving efficiency, and potentially saving resources for patients and the healthcare system [3,7,15,17,37–48]. However, this is not always the case as seen with FDCs for patients with HIV in France and Spain [49].

FDCs can also help clinicians to effectively manage patient outcomes from the perspective of long-term care, allowing them to use combinations of active ingredients that are effective over time and can improve patient safety as seen for instance with FDCs for respiratory conditions and pain-management [23, 50–56]. In addition, potentially reduce costs and improve the co-operation between physicians and patients [17,57], with savings enhanced by the availability of generic FDCs [58]. Co-payment costs can also potentially be decreased with FDCs versus individual components, which is particularly important in lower- and middle-income countries (LMICs) where there are high co-payments [59].

The World Health Organization (WHO) endorses FDCs particularly for infectious diseases such as HIV, malaria, tuberculosis (TB), and Hepatitis B to improve the effectiveness of treatments especially given the toxicity that can exist with antiretrovirals as well as help prevent resistance from developing [15,25,60]. This is particularly important in sub-Saharan Africa with a high prevalence of both non-communicable diseases (NCDs) such as hypertension and diabetes along with infectious diseases including HIV, TB and malaria, and a high prevalence of patients with joint co-morbidities versus other continents [15,61–69]. Having said this, a recent Cochrane review suggested that there was no difference in outcomes with FDCs versus single-drug formulations combined in managing patients with newly diagnosed pulmonary TB [70]. However, others have published different findings (Section 2. 6). In the case of new FDCs for patients with HIV, the dogma of effective antiretroviral therapy (ART) containing at least three active substances is being challenged by new data showing effectiveness with FDCs containing just two medicines, with costs helped by patent expiry and more generic formulations becoming available [71]. Treatment costs can also increase in some settings with the prescribing of multiple medicines over patented FDCs due to higher rates of adverse effects [72].

1.3. Aims and objectives

Given the controversies surrounding the use of FDCs, there is an urgent need to discuss both their advantages and disadvantages including their cost-effectiveness. This is particularly important in LMICs in view of their high prevalence of both

infectious diseases and NCDs, their considerable resource pressures, and the continued growth in both morbidity and mortality from NCDs [73–80]. However, different conclusions concerning the clinical and economic value of FDCs can be drawn from the different disease areas as well as within disease areas depending on the FDCs available within a country. There is also a perceived paucity of published data regarding the costs, value, and cost-effectiveness of FDCs across different disease areas in LMICs versus high-income countries, which needs to be addressed. Consequently, the principal focus of the findings and suggestions in this perspective paper is on the costs, value, and pharmacoeconomics of current and future FDCs aimed mainly at governments and their advisers in LMICs. However, patients also play a key role especially in LMICs where there can be high co-payments and predominant 'out of pocket' payments, and patients' illness can have a catastrophic effect on the rest of the family [81,82].

An iterative process was used to develop this review paper building on pertinent publications known to the coauthors in both infectious diseases and NCDs. These publications were supplemented by suggested activities from the senior level coauthors from across countries and continents on potential ways forward to enhance the prescribing of valued FDCs. This reflects, as mentioned, the envisaged paucity of published pharmacoeconomic data on FDCs in LMICs.

We are aware of ongoing initiatives among several LMICs to strive toward universal health care (UHC) recognizing the challenges. Besides this, ongoing initiatives across LMICs to achieve agreed Sustainable Development Goals (SDGs). The SDGs include a reduction in morbidity and mortality associated with NCDs such as cardiovascular and respiratory diseases [74,83–86]. The availability of pertinent and affordable FDCs can potentially play a key role in achieving these goals alongside educational and lifestyle changes.

1.4. Methodology

We were aware that there have only been a limited number of publications assessing the value of FDCs in LMICs, with most publications typically involving higher-income countries We are also aware that the potential role and value of FDCs also vary between and within disease areas and populations as well as across countries. Consequently, we did not undertake a formal systematic review; however, based this perspective paper, including suggested future activities, on pertinent publications known to the senior level coauthors across multiple LMICs combined with their extensive experiences with FDCs to contextualize the findings.

This perspective paper will be divided into three parts to provide future direction. Firstly, we will briefly review the role and value of FDCs within and across key infectious and non-infectious diseases. Infectious diseases include HIV, TB, and malaria and noninfectious diseases include cardiovascular diseases (CVD) such as hypertension and type 2 diabetes mellitus (T2DM) as well as pain management and respiratory diseases. This also addresses the polypill for patients with CVD [38,40,87].

The senior-level personnel involved in this paper come from a wide variety of backgrounds including government groups, academia, rational use medicine personnel, clinicians, and patient representative groups. A wide variety of LMICs have been included in this perspective paper in terms of their geography, population size, GDP per capita, and progress toward universal health care. We have used such approaches before to stimulate debate in priority disease areas to provide future guidance [88–100]. The 2018 World Bank classification has been used to categorize countries into LMICs or upper-income countries [101] wherever pertinent.

We will start with NCDs including CVD, diabetes, respiratory diseases, and pain management, before discussing the potential role and value of FDCs in patients with high priority infectious diseases including HIV, malaria, and TB. These disease areas are included as they are the subject of most publications regarding the pharmacoeconomics of FDCs across countries and they are the major source of morbidity and mortality within LMICs. We have not included FDCs for patients with Hepatitis C despite being listed in the WHO Essential Medicine List (EML) as a result of their considerable effectiveness and safety versus previous medicines since their prices can be prohibitive for countries and citizens without substantial discounts. This is exacerbated by pharmaceutical companies making up to 99.9% gross profit in some countries adding to the overall cost of medicines [102–106]. Having said this, expenditure on new medicines for patients with Hepatitis C has been helped by the increasing availability of low-cost generics [107], as well as treatments provided free or for limited costs in some countries; however, this is not universal among LMICs [108,109]. Similarly, we have not included topical FDCs for use in dermatology although we are aware that there are concerns with a number of these in LMICs such as India [4,110]. Lastly, we have excluded combination antibiotics such as amoxicillin with an enzyme inhibitor as these medicines should now be reserved under the recent WHO AWaRe list of antibiotics and there can be considerable concerns with their availability [11,12,111–114]. We have though included sulfamethoxazole and trimethoprim FDC to help prevent *Plasmodium falciparum* (Pf) malaria and other infections despite initial concerns that this FDC would impact on the effectiveness of treatments such as sulfadoxine-pyrimethamine due to shared mechanisms of action and resistance pattern development [115]. These concerns, however, have not materialized and this combination is now widely used in malaria-endemic countries as prophylaxis in both HIV-infected children and adults as well as those without HIV [116,117].

Secondly, we will document FDC availability within public health-care systems among a range of LMICs covering multiple countries and continents versus the latest WHO EML. This is because the WHO EML is recognized as a guide to the development of national and institutional EMLs with medicines selected for national lists with due regard to disease prevalence and public health relevance in a country as well as evidence of clinical efficacy and safety, comparative costs and cost-effectiveness in a country [111,118,119].

We will also try and explain any variability in the availability of FDCs between countries as a prelude to lastly discussing their advantages and disadvantages as well as potential ways forward to enhance their prescribing where pertinent. These

deliberations will be based on the perceived value, or lack of it, of FDCs across the chosen disease areas among the senior level coauthors. We will also seek to guide key stakeholder groups in LMICs going forward given the lack of pharmacoeconomic data to date to make future policy decisions. We will also describe potential measures to reduce the prescribing of FDCs where there are concerns. We have undertaken this approach to address the paucity of published studies addressing the pharmacoeconomics of FDCs in LMICs versus high-income countries despite the high prevalence of both infectious and noninfectious diseases in these countries.

2. Role and value of FDCs across disease areas including health economic evaluations

We will start with a review of the role and value of FDCs in patients with NCDs followed by high priority infectious disease areas including HIV, malaria, and TB. This will include a consolidation of studies that have been published in LMICs regarding the pharmacoeconomics of FDCs in these chosen disease areas.

2.1. Cardiovascular diseases (CVD)

Improved management of CVD is seen as critical with CVD a leading cause of morbidity and mortality globally as well as causing a high economic burden to health-care systems [120,121]. Reducing the morbidity and mortality due to CVD is particularly relevant in lower-income countries and areas with under-developed/equipped health-care systems where rates have increased in recent years exacerbated by changes in lifestyle, diet, and urbanization [122–128].

Management strategies for CVD and hypertension largely involve encouraging changes in lifestyle as well as prescribing medicines from several pharmacological classes. Consequently, CVD and hypertension may be good candidates for the development and use of FDCs, with a number of FDCs currently in use globally.

Overall, FDCs are thought to be a potential solution to the high pill burden seen in some patients with CVDs, including those with hypertension, increasing adherence, and the clinical effectiveness of prescribed medicines [20,35,37,45,57,126,129–139]. A key highlight of the 2018 European Society of Cardiology and European Society of Hypertension (ESC/ESH) guideline on the treatment of hypertension is the single-pill treatment strategy with the preferred use of a single pill combination for most patients to improve their blood pressure (BP) control [135,140]. FDCs also offer the potential to combine the additive effects of different treatment approaches without having to appreciably increase the dose of individual medicines, which could increase their side-effects and potentially decrease adherence in routine care [37,141,142].

FDCs can also transform the management of patients with CVD including hypertension by reducing the need for titration and adding in different classes of medicines to help control patients' BP [143]. This is particularly important in LMICs where the costs of transport and loss of income attending health-care clinics can adversely affect their attendance and goal attainment [144,145], with medication follow-up visits among patients with CVDs already a major issue particularly in Africa [144–146]. There are ongoing programs across LMICs to address concerns with adherence to medicines including instigating adherence clubs as well as educational and other programs for patients given concerns with the educational level of patients with CVD in a number of LMICs [144,145,147–150]. FDCs can help with this as well as help reduce the potential for stock-outs by limiting the number of medicines that need to be available among primary health-care centers [151]. Consequently, FDCs can be viewed positively by all key stakeholder groups including physicians, pharmacists, and patients [143,152,153]. Other factors positively influencing the perception of FDCs include health authority policies toward FDCs and their costs if these are reduced especially when there are high co-payments [152]. Their use, however, does vary between health-care systems for many reasons including clinician/patient preferences, their costs, and healthcare system approvals [41,154,155]. There have also been differences in outcomes between FDCs for CVDs as well as when doses are missed [156,157].

The renin-angiotensin system (RAS) blockers are seen as a core component of FDCs for patients with hypertension except where they are contraindicated [158,159]. Typically, thiazide diuretics or calcium channel blockers (CCBs) should be used as first-line treatment especially in sub-Saharan Africa with RAS blockers – angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) – potentially added in as a single FDC [35,159–161]. However, ACE inhibitors have a more limited effect in reducing blood pressure in the black population and their prescribing needs to be more carefully managed in this population [160,162]. Diuretics can though enhance the effect of RAS blockers whilst minimizing their undesirable metabolic effects, whilst CCBs and RAS blockers have synergistic protective effects on the vascular wall and have been shown to be effective FDCs when combined improving adherence and outcomes [159,163,164]. ACE inhibitors may also offset one of the major side effects associated with CCBs which is pedal edema [165]. In any event, the management of patients with hypertension is a priority area in LMICs including sub-Saharan Africa with often patients needing two or more medicines following titration [144,160,166,167].

Studies assessing the costs and cost-effectiveness of FDCs in CVD have principally been performed in high-income countries. These include studies by Sherrill et al. (2011) demonstrating health-care costs were appreciably lower in the FDC group compared with those patients taking the medicines separately [168]. A study in Canada also showed yearly medicine cost savings with FDCs [169], and a study in Japan also showed significant medicine cost savings with FDCs versus patients taking multiple tablets [170]. Other published studies involving high-income countries have also shown significantly lower costs for FDCs in CVD versus multiple tablets [45,171–174]. However, Deshmukh et al. (2017) in the US found the acquisition costs for FDCs were higher among patients being treated for their hypertension versus free-pill combinations although the higher costs were more than offset by lower inpatient costs [43].

There can though be concerns if FDCs include combination drugs with similar mechanisms of action such as combining an ACE inhibitor with an ARB, which increases adverse events and costs without any obvious additional clinical benefits [175]. In addition, we have seen some LMICs flooded in recent years with multiple FDC anti-hypertensive medicines not listed in the WHO EML and concerns with their rationality [1,36,176]. Having said this, combinations of anti-hypertensive medicines are typically needed in LMICs, especially in sub-Saharan Africa, given the high prevalence of hypertension as well as resistant hypertension that can exist in these countries [144,149,160,167,177]. However, the nature of the anti-hypertensive medicines in the various combinations can be important especially given, as mentioned, concerns with ACE inhibitors and ARBs among the black population [160,162]. A recent meta-analysis showed that lowering BP by 10 mmHg resulted in a 20% reduction in the risk of major cardiovascular events. However, despite various anti-hypertensive classes reducing specific clinical outcomes, i.e. diuretics appearing more effective for heart failure and CCBs more effective for stroke prevention with beta-blockers and ACE-inhibitors not ideal, overall all classes of anti-hypertensives had similar effects in reducing major cardiovascular disease [178].

Currently, four groups of anti-hypertensive FDCs are listed in the WHO EML (21st Edition 2019). These include an ACE inhibitor plus a CCB, ACE inhibitor plus a thiazide or thiazide-like diuretic, ARB plus a CCB and an ARB plus a thiazide or thiazide-like diuretic [111]. However, since lisinopril is preferred over other ACE inhibitors, telmisartan over other ARBs, amlodipine versus other once-daily CCBs, and hydrochlorothiazide (HCTZ) over other similar diuretics, the current 21st WHO EML lists lisinopril plus amlodipine, lisinopril plus hydrochlorothiazide, telmisartan plus amlodipine and telmisartan plus hydrochlorothiazide [111]. This is in line with treatment guidance that recommends initiation with at least two anti-hypertensive medicines for those patients with markedly elevated blood pressure, and follows prior concerns about the limited availability of FDCs in the WHO EML [179–181].

There have also been combinations of statins and anti-hypertensives to help reduce CV events including FDCs of amlodipine and atorvastatin. However, there have been mixed findings regarding their effectiveness including increased adherence as well as costs versus single tablets combined [17,139,182–185]. Currently, no FDC containing a statin and an anti-hypertensive is listed in the WHO EML [111].

Besides this, there have also been FDCs containing different lipid-lowering medicines including ezetimibe combined with either simvastatin, atorvastatin, or rosuvastatin [186–190]. The belief is that by combining different lipid-lowering medicines with different mechanisms of action adherence can be enhanced along with improved effectiveness and outcomes [191]. However, there have been concerns among health authorities regarding the effectiveness of ezetimibe in reducing CV events in reality, which has limited its use in practice [192,193]. Currently, no FDCs containing combinations of different lipid-lowering treatments with different mechanisms of action are listed in the WHO EML, potentially reflecting some of the controversies seen [111].

There are also FDCs containing lipid-lowering medicines and oral antihyperglycemic agents (AHAs) to try and improve outcomes in patients with both dyslipidemia and T2DM through reducing the pill burden [194]. However, currently, no FDCs containing a statin and AHA are listed in the WHO EML [111].

Attention in recent years has turned to the development and availability of a 'polypill', which is an oral tablet containing low dose aspirin, a statin, and at least one anti-hypertensive medicine to prevent CV events [195]. Such a pill is potentially seen as an affordable and cost-effective for the prevention of CVD especially in LMICs if the polypill was made available based on current public sector prices [38,40,42,143,196–199]. Polypills have also been shown to enhance adherence, are well tolerated and reduce risk factors in both primary and secondary prevention [87,196,200–202]. However, there are concerns that a single polypill may not be suitable for all patients and it could well be necessary to develop several different types of polypills to meet the needs of all patients to maximize effectiveness and efficiency [203,204]. In addition, the availability of FDCs has to be balanced against the increased risk of duplication of medicines among hypertensive patients being prescribed FDCs and concerns with prescribing a polypill initially without titration [87,205].

2.2. Type 2 diabetes mellitus (T2DM)

First-line treatment in patients with T2DM is typically metformin [46,206–209], with the subsequent initiation of additional oral antihyperglycemic agents (AHAs) if patients fail to achieve target HbA1c levels. FDCs have been developed to reduce the pill burden as well as potentially enhance adherence and outcomes in patients with T2DM [46,210–212], with reduced pill burden along with improved effectiveness and reduced side-effects welcomed by patients [213]. Poor control of patients with T2DM is a concern especially among African countries [162,214–217].

FDCs include those with a sulfonyl urea (SU) and metformin, metformin and acarbose, DPP-4 (dipeptidyl peptidase-4) inhibitors and metformin, thiazolidinedione and metformin, alogliptin and pioglitazone, sodium-glucose transport protein 2 (SGLT2) inhibitors and metformin, and a SGLT2 inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor [210,218–220]. FDCs containing metformin and a DPP-4 inhibitor, as well as metformin and SGLT2 inhibitors are seen in particular as providing metformin with complementary mechanisms of action to improve glycemic control whilst reducing the pill burden, and similarly with saxagliptin/dapagliflozin FDCs [218,221–224].

In their systematic review principally involving high-income countries, Vijayakumar et al. (2017) found improved adherence with FDCs leading to improved effectiveness [225]. However, it was difficult to determine the actual level of clinical significance with no studies appearing to randomize patients to either the FDC or the separate components [225]. Lokhandwala et al. (2016) suggested that improved adherence and compliance with FDCs may well translate into reduced health-care utilization and costs in the US [226]. However, there are issues of affordability in LMICs, especially with the newer oral anti-diabetic medicines.

There are also concerns with both published and unpublished clinical trial data of five metformin containing FDCs in India which currently account for 80% of all metformin sales [27]. Concerns include the limited number of patients in the clinical trials, which

typically were not conducted in India, and whether improved health gain is seen for the FDC versus co-prescribing the individual components together. Evans et al. (2015) were also concerned with the typical length of follow-up in clinical trials with for instance one study involving only 40 patients followed up for just 2 weeks [27]. In their critique of Evans et al. though, Kannan et al. (2015) stated that SU/metformin FDCs are particularly popular among general practitioners and patients in India as they contain lower doses of metformin to reduce or stop gastrointestinal side-effects as well as result in a rapid decrease in blood glucose concentrations. However, the relatively high doses of SUs used in the FDCs increases bodyweight worsening insulin resistance and reversing the beneficial CV effects when metformin is prescribed first line in higher doses [59]. In view of this, Kannan et al. recommended using each medicine separately and titrating doses accordingly [59]. This though can be a challenge in India with current high patient co-payments as the cost of the FDCs can often be cheaper than the combined costs of the separate tablets [59].

The disadvantages of FDCs can include difficulties with determining the cause of poor effectiveness and/or the side effects of treatment, patients' refusal to accept their disease if FDCs are prescribed as initial treatment instead of for instance metformin, and potentially higher costs [227].

Currently, no FDC for patients with T2DM is currently listed in the WHO EML [111], and there are issues with the affordability of most of these FDCs in LMICs.

2.3. Respiratory diseases

In patients with asthma, treatment strategies using combination inhalers of corticosteroids (ICS) and long-acting β agonists (LABAs) are seen as the most effective and safe approach to prevent exacerbations [228–231]. For instance, Tohda et al. (2010) demonstrated that the FDC of fluticasone and salmeterol resulted in a higher proportion of totally controlled weeks per patient with asthma versus fluticasone [232]. This builds on guidelines advocating the use of such combinations [231,233]. This was based on the evidence that LABAs can potentially increase the risk of mortality if used in patients with unstable asthma without the concomitant use of ICS therapy [233,234].

Published studies have also compared the effectiveness of ICS (fluticasone) and LABA (salmeterol) FDCs with other inhaled ICS containing regimens including LABAs in patients with chronic asthma. In the UK, Doull et al. (2007) ascertained that in adults, this FDC was cheaper than increasing the dose of fluticasone, and in children, the FDC was similarly effective compared with fluticasone plus salmeterol in separate inhalers; however, its use resulted in annual cost savings of between GB£47 and GB£77 per child based on UK costs [235]. Studies in Canada have investigated the cost/QALY of the fluticasone/salmeterol FDC [236], and in Japan, Tohda et al. (2010) demonstrated that the FDC of fluticasone and salmeterol resulted in lower mean direct management costs [232]. Previously, Jonsson et al. (2004) in Sweden had demonstrated that a budesonide (ICS) and formoterol (LABA) FDC had improved effectiveness and lowered costs versus separate inhalers [237]. These though are all studies from high-income countries.

Currently, only one ICS/LABA combination (budesonide and formoterol) is included in the WHO EML [111]. This reflects the fact that the listed medicines within the WHO EML should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing with no overall difference in terms of efficacy and safety data between the various FDCs available. In addition, the listed medicine or FDC is generally available at the lowest price based on international drug price information sources [111].

LABA/ICS FDC inhalers have also been used in patients with chronic obstructive pulmonary disease (COPD) with studies assessing their effectiveness as well as their cost-effectiveness across countries including LMICs [238–244]. However, recently there are concerns with an increased risk of serious pneumonia with LABA/ICS FDCs resulting in guidance that they should only principally be given to COPD patients with asthma-like symptoms [23,245,246]. However, this combination is still being prescribed despite concerns [247].

The costs of LABA/ICS FDC inhalers have started to come down among high-income countries with an increasing use of lower-cost FDCs combined with initiatives to reduce the steroid burden and improved monitoring of patients [23,231,248]. This should further enhance their cost-effectiveness as well as their access among LMICs.

We have not included any evaluation of FDC inhalers containing an ICS plus a short-acting β agonist (SABA), with ICS typically recommended as first line treatment for patients with asthma before moving onto an ICS/ LABA FDC for maintenance therapy [231]. As a result, limited use of ICS/ SABA combinations across countries and also discontinuations [23].

LABA/long-acting antimuscarinic agent (LAMA) FDC inhalers also appear beneficial with enhancing bronchodilation in patients with COPD uncontrolled on single agents [50,249–254]. This builds on GOLD guidance which recommends that when a single bronchodilator fails to achieve the desired outcome a second bronchodilator from a different class may be added [249]. There have also been studies assessing the costs and cost-effectiveness of LABA/LAMA FDCs typically in high-income countries [249,255–257]. However, currently, LAMAs are unaffordable in a number of LMICs including the public health-care system in South Africa. It is hoped that as more formulations are launched, costs will come down to more affordable levels to enhance access.

It is recognized that pharmacists and other professionals can assist in lowering the costs of medicines to treat patients with COPD through education and improved adherence [258,259]. These activities, coupled with lower costs of inhaler FDCs as different combinations are launched competing with others, should further enhance their use and improve patient care in a cost-efficient manner.

2.4. Pain

Combinations of medicines may often be needed for pain management, especially severe pain, with often a 'multimechanistic' approach needed [53]. As a result, a combination of analgesics or an FDC containing analgesics with different mechanisms of action may be needed to increase the effectiveness and/or reduce the

side effects versus increasing the doses of single agents alone [53]. This is seen with the FDC of acetaminophen/ibuprofen in patients with moderate to severe postoperative dental pain where the combination provided greater and more rapid analgesia than comparable doses of either agent alone [56]. Besides this, FDCs of tramadol and paracetamol may be opioid sparing without sacrificing effectiveness, which is seen as important given some of the recent concerns with tramadol especially its potential for abuse [260–263]. In addition, a tramadol/paracetamol FDC can present a potential alternative to nonsteroidal anti–inflammatory drugs (NSAIDs) in the elderly reducing concerns with possible gastrointestinal side-effects [264].

In their study, Cristancho et al. (2013) found that an FDC of acetaminophen and codeine (AC) had lower cost and was more effective in reducing pain within the first hours after administration versus an acetaminophen and hydrocodone (AH) FDC or an acetaminophen plus tramadol (AT) FDC [265]. The costs/numbers needed to treat for each formulation were $1816 Colombian pesos/2.2 for AC, $4772 Colombian peso/2.3 for AH, and $5342/2.6 for AT. Using AC as the comparator, the ICER for AT from a payer's perspective was $8790 Colombian pesos and $29,640 Colombian pesos for AH [265].

FDCs of paracetamol and NSAIDs may also offer superior analgesia effects compared with either medicine alone [55]. This is important especially in the elderly resulting in calls to develop an FDC of NSAIDs combined with a gastroprotective medicine such as a proton pump inhibitor or a high-dose histamine-2 receptor antagonist [266].

There are concerns though regarding FDCs for management of pain. Many of these medicines are misused or dangerous in overdose and currently no FDC for pain management is included in the WHO EML [111]. In addition, there are concerns that the general principles of pain management may be compromised by high use of FDCs including adhering to the general principles for the management of chronic pain [267].

2.5. Malaria including prevention

Both dihydroartemisinin-piperaquine (DP) and sulphadoxine-pyrimethamine (SP) have been used for malaria prevention in pregnant mothers, with a recent review suggesting that intermittent preventive treatment may reduce maternal and placental malaria and that monthly DP appears more effective than SP in reducing placental malaria [268].

There are also ongoing initiatives with DP combinations to improve their packaging to facilitate correct use to further improve their overall effectiveness and value, with published studies showing a single course treatment for uncomplicated falciparum malaria is well tolerated [269,270]. Assi et al. (2017) have also demonstrated that the artesunate–amodiaquine FDC is well tolerated to treat uncomplicated PCP malaria under real-life conditions [271], with this combination now widely used. Banek et al. (2018) have shown that co-formulated artemether–lumefantrine (AL) and fixed dose amodiaquine–artesunate (AQAS) have high self-reported adherence rates among children [272]. Overall, AL was less likely to be taken correctly at one of the study sites; however, it was better tolerated overall than AQAS which may enhance its overall utility in routine clinical care [272]. Itoh et al. (2018) found the artemether-lumefantrine FDC effective in treating uncomplicated *P. falciparum* malaria among Brazilian patients in the Amazon jungle, strongly supporting the continued use of this FDC as a first-line therapy [273]. Recently Ebenebe et al. (2018) compared the effectiveness of 3-day regimens of AL, artesunate-amodiaquine (AA), and DP among 910 under-five children in Nigeria. The authors found all three evaluated treatments were effective in the management of uncomplicated malaria in young children; however, DP appeared slightly more efficacious than either AL or AA [274].

Studies are also ongoing to increase the dose of DP and extend the dosing schedule to four monthly doses to reduce the incidence of malaria especially during the high transmission season, and this may well continue to enhance the value of this FDC [275].

Artemisinin-based combinations or chloroquine in combination with a short course of primaquine have also been shown to be highly effective in the treatment of vivax malaria in Brazil [276]. An FDC of mefloquine combined with artesunate has also been studied in cases of falciparum malaria in the Brazilian Amazon basin and shown to have acceptable efficacy, safety, and tolerability [277]. However, artesunate–mefloquine FDCs have been used infrequently in Africa due to a perceived poor tolerance to mefloquine although recent studies in children in Africa are now suggesting otherwise [278].

There are concerns though with the number and availability of unapproved FDCs to treat malaria among LMICs with recent estimates suggesting almost half of the sales value and volume of antimalarials are generated by unapproved products [279]. This calls for tighter regulatory process to avoid patient harm as well as appropriate training of pharmacists and their assistants when treatments are dispensed without a prescription [62]. There are also concerns about the pharmacokinetic profile of some FDCs for malaria, which again requires further attention going forward.

Overall though, FDCs are routinely used to prevent and manage patients with malaria due to their effectiveness and tolerability, and this will remain. This is endorsed by the WHO, with six FDCs for malaria and its prevention currently included in the WHO EML [111]. However, there is a paucity of information regarding the costs of treating patients with malaria as well as the cost-effectiveness of FDCs. Ezenduka et al. in 2017 estimated the costs of treating uncomplicated malaria at a public health-care facility in Nigeria [280]. A recent study in Tanzania suggests that AL and DP as the first- and second-line treatment, respectively, for patients with malaria will save approximately US$64,423 per year whilst achieving a 3% reduction in the number of malaria cases compared with AL plus quinine [281]. However, a policy that uses DP as the first-line anti-malarial medicine will consume an additional US$780,180 per year whilst achieving a further 5% reduction in the number of malaria cases versus AL followed by DP [281].

Key areas of pharmacoeconomic research in the future will also center around funding monthly prophylaxis versus focused screening and treatment of identified cases [282]. In addition, assessing the simultaneous use of artemether-lumefantrine, artesunate-amodiaquine, and dihydroartemisinin-piperaquine FDCs against strategies in which these treatments would be cycled or used sequentially [283].

2.6. Tuberculosis (TB)

The treatment regimen for TB can be problematic with patients required to take four medicines during the two-month intensive phase followed by a continuation phase of 4 months with two medicines adversely affecting patient adherence in practice [284–286]. These concerns have resulted in the development of FDCs to enhance adherence rates and reduce default rates. In a study from Brazil by Braga et al. (2015), FDCs containing rifampin (R), isoniazid (H), and pyrazinamide (Z) combined with ethambutol (E) reduced default rates and halted the potential increase in resistance rates compared with an FDC of RH plus pyrazinamide separately [287]. However, a previous meta-analysis published in 2013 failed to show any difference in the acquisition of drug resistance, bacterial conversion rates after 2 months of treatment, or the incidence of adverse drug reactions between patients on FDCs versus administering the medicines separately [288]. Gallardo et al. (2016) came to similar conclusions in their Cochrane review [70]. Lima et al. (2017) also found that four-medicine FDCs did not improve culture conversion after 2 and 6 months of treatment versus the separate medicines; however, the FDCs provided greater patient comfort by reducing the pill burden as well as reducing gastrointestinal adverse effects [289].

In Brazil, the FDC containing rifampicin, isoniazid, pyrazinamide, and ethambutol (HRZE) has been available since 2009 produced by local laboratories through a Partnership for Productive Development Agreement [290]. In spite of the methodological limitations casting doubt on the findings [291], an interrupted time series evaluating patient outcomes with this FDC found no difference in treatment abandonment rates although there was a trend toward decreased cure rates [292].

Overall, FDCs can simplify treatment regimens, which may be important in some patients, along with instigating therapeutic drug monitoring (TDM) in selected patients to help detect non-adherence early as well as help manage potential drug:drug interactions [293]. Having said this, TDM is likely to be unavailable or unaffordable in most LMICs. Strategies to further enhance adherence rates include opening more treatment centers as well as community outreach centers in rural areas where access is a concern [294]. This builds on strategies to provide standardized anti-TB drug regimens free of charge to all patients administered under direct observation to improve patient outcomes combined with other measures such as patient support [63,295]. We are also seeing in South Africa standard operating procedures instigating enhanced adherence counseling in patients with continued positive smear tests [296,297], and this is continuing.

There can though be concerns with FDCs for patients with TB. These include concerns with poor bioavailability with some FDCs including those with rifampicin as well as concerns when some patients are switched between different rifampicin formulations without adequate monitoring. In addition, concerns with enzyme level elevations, increases in adverse drug reactions with some combinations, concerns with adverse drug reactions with certain FDCs for patients with both HIV and TB, as well as issues associated with TDM and dose adjustments especially with rifampicin [18,298]. Having said this, the WHO currently endorses five FDCs for the treatment of TB in its EML [111].

2.7. Human immunodeficiency virus (HIV)

FDCs are also increasingly used in patients with HIV to reduce the pill burden, with studies showing a lower pill burden with FDCs appreciably enhances adherence rates. This is helped by greater patient preference for FDCs as well as improved outcomes including greater viral suppression and improved health-related quality of life (HRQoL) [44,299–309]. However, there is a large variability in the individual components of FDCs used to treat patients with HIV, which can confound the associations reported. As a result, the increase in adherence due to FDCs is not consistently transposed to improving patient outcomes with mixed results reported for viral suppression rates [310] and health-related quality of life (HRQoL) [311]. Key aspects associated with lower HRQoL included being single, smoking, and having co-morbid disease [311].

The WHO endorses the use of FDCs containing tenofovir/lamivudine/dolutegravir (TLD) due to their improved tolerability and effectiveness, a reduced risk of resistance acquisition, lower discontinuation rates, and fewer drug interactions [312,313]. Meireles et al. (2019) in Brazil also found that a TLD combination of TDF/3TC (tenofovir/lamivudine) combined separately with dolutegravir (DTG) was more effective in suppressing viral load than a tenofovir/lamivudine/efavirenz (TLE) FDC, which was not driven by higher adherence rates [314]. As a result, Phillips et al. (2018) modeled that DTG containing combinations is predicted to be both effective and cost-effective among sub-Saharan African countries [315]. Zheng et al. (2018) also found that a generic DTG-based regimen is likely to be cost-effective in India; consequently, they believed this regimen should be recommended as initial therapy in patients newly diagnosed with HIV in India [316]. Having said this, there are still concerns regarding DTG and its combinations among LMICs. These include the need for further studies to better determine the risk of adverse birth outcomes when DTG is initiated pre-conception as well as assessing its effectiveness when co-administered with treatments for patients with TB [317]. However, there are ongoing studies assessing the optimal dosing regimen of DTG with rifampicin as well as its safety in pregnant women helping to address these concerns [313,318–320]. The interactions between efavirenz and bedaquiline are a problem for patients with HIV who have M/XDR-TB and who are taking bedaquiline containing FDCs. These patients need to be switched from a generic efavirenz-containing FDC regimen to twice-daily nevirapine with separate companion pills to address concerns [321]. These patients also need to be closely monitored following switching to other antiretroviral (ART) FDCs as there can subsequently be low ART adherence in these patients [321]. Patient monitoring should happen generally when patients are switched between ARTs.

Studies typically undertaken in high-income countries have shown that FDCs prescribed first-line are generally seen as more effective and less costly than other regimes [302,308,322–324]. Cohen et al. (2013) in the US found lower pharmacy costs, fewer hospitalizations, and lower hospital costs in patients prescribed FDCs, which resulted in significantly lower overall total health-care costs [32], with a study in Spain suggesting overall costs will increase with multiple tablet regimens versus FDCs due to a greater prevalence of adverse drug events [72]. Colombo et al.

(2014) in Italy also found lower costs for FDCs [33]. However, Angeletti et al. (2014) in Italy found only a 1.5% reduction in average annual costs with FDCs versus multiple drug regimens [325]. Contrasting this, Libre et al. (2018) demonstrated greater efficiency for multiple tablets combined in patients with HIV in France and Spain versus FDCs, which was mainly due to similar effectiveness but lower direct costs with multiple tablets [49]. These differences may be sensitive to the availability of generic formulations [49,58].

Among LMICs, in Brazil, a cost analysis per responder was performed alongside a cohort study (J Costa unpublished data) and the authors found the mean annual cost per patient initiated on an FDC was lower than for those prescribed multiple tablet regimens [301]. This was mainly due to lower costs of ART and lower switching rates. There was though no difference in effectiveness rates between groups after 12 months of treatment although overall a better cost-effectiveness ratio for the FDC [326].

Overall, FDCs for patients with HIV are well accepted and endorsed in the WHO EML [111]. Careful consideration is needed when the manufacturers of the different components of FDCs lower their unit costs potentially affecting overall prices and cost-effectiveness of FDCs versus multiple tablet regimens. Sweet et al. (2016) found that overall costs increased in the US with patented FDCs versus generic multiple drug regimens despite lower in-patient costs due to acquisition cost differences [327].

There are also calls to develop a cotrimoxazole and isoniazid FDC together with pyridoxine to help prevent TB from developing in patients with HIV as a cost-effective option [328].

2.8. Infectious diseases treated with antibiotics

We have not included combination antibiotics such as amoxicillin combined with an enzyme inhibitor in this paper as these medicines should be reserved under the recent WHO AWaRe list of antibiotics and there can be considerable concerns with their availability and use [11,12,111–114]. Consequently, the prescribing and dispensing of these FDCs should not be encouraged but restricted.

2.9. Consolidated pharmacoeconomic findings in LMICs

Table 1 contains details of published studies regarding the cost-effectiveness of FDCs among LMICs contained in Sections 2.1 to 2.8. Typically, there are considerably more published studies regarding FDCs for NCDs among higher-income countries versus LMICs.

In view of the comparative lack of pharmacoeconomic studies regarding FDCs in LMICs coupled with ongoing concerns, there is a need to consider both the positive points and concerns regarding FDCs among senior-level personnel in a range of LMICs to provide guidance regarding their future role and value as well as potential ways forward.

2.10. FDC availability across LMICs by disease area

Table 2 contains details of FDCs available in the public sector, which means full or partial reimbursement from public sources, across a wide range of LMICs. This includes FDCs within the WHO EML as well as other FDCs within the country. Typically, where there are both private and public markets in a country, there is greater availability of FDCs in the private market, e.g. Brazil, South Africa, and Sudan, with typically no reference to the WHO EML. The exception can be for medicines for malaria, TB and HIV where in some countries these are dispensed free of charge in the public sector with the help of the Global Fund, e.g. Sudan.

The differences in the availability of different FDCs within and between the different countries reflect differences in the prevalence of infectious diseases between countries especially for malaria and TB. In addition, the priority for respiratory diseases versus CV disease, the potential wealth of the country especially regarding the number of FDCs for CV diseases, as well as the extent of regulatory control. For instance, we have not included India in Table 2 in view of the appreciable number of FDCs still available in the country, which are often irrational, although this is starting to change [1,14,27–29,36]. Concerns with the prescribing of FDCs in India was emphasized in the study by Balat et al. (2014) where only 5.8%, 9.8%, and 10.9% FDCs prescribed by physicians in Ahmedabad city were included in the WHO EML (2010), National (2011), and Gujarat State (2011) EML, respectively, [330]. Overall in India, there have been 98 different FDCs for CV diseases including hypertension, 26 FDCs for T2DM, 12 inhaler FDCs for patients with respiratory diseases including formoterol and budesonide, and 24 FDCs for the management of pain. There have also been 9 FDCs for malaria including 5 on the WHO EML, 5 FDCs for malaria including 2 on the WHO EML and 18 FDCs for HIV including one on the WHO EML (Table 2). As a result, there is an urgent need to sensitize physicians and undergraduates to potential concerns with the irrational prescribing of FDCs where pertinent (Box 2) [331]. This is beginning to happen in India with, as mentioned, a significant reduction in the number of FDCs available (328 in all) in recent years [29].

2.11. Positive and negative issues with FDCs across disease areas

Table 3 contains general positive clinical and economic considerations associated with FDCs that enhance their pharmacoeconomic profile, which is based on the perspectives and experiences of the senior level coauthors from multiple LMICs. Table 4 contains details of additional benefits for the different infectious and noninfectious disease areas where FDCs are typically prescribed.

Tables 5 and 6 contain concerns that the senior level coauthors have regarding FDCs, which are both general and disease specific.

Box 1 contains suggestions for possible activities that can be undertaken within countries to enhance the prescribing of valued FDCs given the concerns that have existed regarding FDCs with appreciable variability in their availability among LMICs (Table 2). Potential activities include a greater role for patients and patient organizations to enhance the prescribing and adherence to valued FDCs to enable patients to attain and retain treatment goals especially those with chronic NCDs [332]. In addition, helping to ensure FDCs are produced at

Table 1. Published pharmacoeconomic studies of FDCs in LMICs.

Author, year and country	FDCs and methods	Principal findings
Non Communicable Diseases		
Cardiovascular disease		
Gaziano et al (2006) – multiple countries [329]	• 2 FDCs – one containing aspirin, lovastatin lisinopril, and amlodipine (forerunner to the polypill) for primary prevention and a similar FDC for secondary prevention with metoprolol replacing amlodipine among six regions involving LMICs • Costings based on the International Drug Price Indicator Guide	• Preventive strategies could result in a 2-year gain in life expectancy • ICERs for secondary prevention ranged from 306 USD/QALY to 388 USD/QALY gained.
Sing et al (2018) – India [38]	• Polypill for secondary prevention in India versus usual care groups • The price of the polypill was constructed using a range of scenarios: $0.06 to $0.94/day.	• The mean cost per patient was significantly lower with the polypill strategy at -203 USD per person (95% CI: −286, −119, $p < 0.01$) • ICERs ranged from a cost-saving to $75 per 10% increase in adherence for the polypill priced at $0.94/day
Lin et al (2019) – multiple countries [40]	• Polypill containing aspirin, lisinopril, atenolol, and simvastatin • Microsimulation models used to assess its cost-effectiveness for secondary prevention versus current care in China, India, Mexico, Nigeria, and South Africa • Variety of sources used for prices including retail market prices	• At public-sector prices, the ICER was Int168 USD per DALY averted in China, Int$154 in India, Int$88 in Mexico, Int$364 in Nigeria, and Int$64 in South Africa, amounting to 0·4–6·2%/capita GDP in these countries • The ICER increased to 3·3–14·6%/capita GDP at retail market prices
T2DM	None identified	
Respiratory Diseases – Altaf et al (2015) – India [242]	• Prospective observational study undertaken to evaluate the clinical and economic consequences of salmeterol/fluticasone (SF) – Group I, formoterol/budesonide (FB) – Group II, and formoterol/fluticasone (FF) – Group III – in severe and very severe chronic obstructive pulmonary disease patients • 90 COPD patients were divided into three groups [**NB – No longer recommended** [23,245,246]].	• The 3% and 2% increase in FEV_1 in Groups I and II, respectively, was highly significant vs. 0.2% increase in Group III • The mean total costs over 6 months was Rs. 29,725/- for Group I, Rs. 32,602/- for Group II, and Rs. 37,155/- for Group III • The incremental cost-effectiveness of FB versus SF was Rs. 37,781/- per avoided exacerbation and Rs. 661/-per symptom-free day
Pain management – Cristancho et al (2013) – Colombia [265]	• The cost-effectiveness of three different FDCs indicated for moderate and severe acute pain – acetaminophen 500 mg + codeine 30 mg (AC), acetaminophen 500 mg + hydrocodone 5 mg (AH) and acetaminophen 325 mg + tramadol 37.5 mg (AT) • Prices typically Institutional prices	• The prices/numbers needed to treat were $1816Colombian pesos/2.2 for AC, $4772 Colombian peso/2.3 for AH and $5342/2.6 for AT • Using AC as the comparator, the ICER for AT from a payer's perspective was $8790 Colombian pesos and $29,460 Colombian pesos for AH
Infectious diseases		
Malaria		
Mori et al (2016) – Tanzania [281]	• Dynamic Markov decision model developed • Model based on clinical and epidemiological estimates to predict the budget impact of DP as either first- or second-line treatment alongside AL	• Prescribing AL and DP as first- and second-line treatment, respectively, will save approximately $64,423/year whilst achieving a 3% reduction in the number of malaria cases versus AL + quinine • Prescribing DP as first line will add $780,180/year but achieve a further 5% reduction in the number of malaria cases vs. AL followed by DP
TB	None identified	
HIV		
Zheng et al (2018) - India [316]	• 1 FDC (EFZ/TDF/3TC) vs. TLD (DTG + TDF/3TC) • Microssimulation model	DTG + TDF/3TC is cost-effective with an ICER = 130 US$/life year saved
Costa (2019) – Brazil [326]	• 1 FDC (EFZ/TDF/3TC) vs. multiple tablet regimens with the same formulation of the FDC and other multiple tablet regimens • Cost per responder at 52 weeks • Adjusted for loss to follow-up	FDC was cost-effective with an ICER of US$19583 for multiple tablet regimens with the same composition of the FDC and US$41,128 for other multiple tablet formulations

ACE, angiotensin-converting enzyme; AL, artemether–lumefantrine; DALY, disability-adjusted life-year; DP, dihydroartemisinin-piperaquine; DTG, dolutegravir; EFZ, Efavirenz; FDC, Fixed dose combinations; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

low costs, which is especially important where there are issues of access and high co-payments, combined with incentives to enhance their development and availability [333]. Finally, there is a great need for more published studies and health technology assessments demonstrating their value in LMICs given the current paucity of studies to date (Table 1).

Box 2 documents potential activities that can be undertaken to reduce or negate the availability and prescribing of FDCs of limited value and/or where there are concerns with their irrationality.

2.12. Limitations

We are aware of a number of limitations to this paper. These include the fact that we did not undertake a systematic review for the reasons stated. As a result, there may be some biases in our findings. However, we tried to negate this through using senior-level academic and health authority personnel from across an appreciable number of LMICs to give guidance on potential publications regarding FDCs across multiple disease areas to

Table 2. Availability of FDCs among the various LMICs (Public sector only and only oral medicines apart from inhalers).

	Albania	Botswana	Brazil	Bulgaria	Cameroon	Estonia	Ghana
Infectious diseases							
Antibiotics (Prevention malaria, etc)							
sulfamethoxazole + trimethoprim	Yes	Yes	Yes	Yes	Yes	Yes	Yes
HIV FDCs							
abacavir + lamivudine	No	Yes	No	Yes	Yes	Yes	Yes
dolutegravir + lamivudine + tenofovir	Yes	Yes	No	No	No	No	No
efavirenz + emtricitabine + tenofovir	No	Yes	No	No	Yes	No	Yes
efavirenz + lamivudine + tenofovir	No	Yes	Yes	No	Yes	No	Yes
emtricitabine + tenofovir	No	Yes	Yes	Yes	Yes	Yes	Yes
lamivudine + nevirapine + zidovudine	No	Yes	No	No	Yes	No	Yes
lamivudine + zidovudine	No 6 other FDCs available	Yes 3 other FDCs	Yes 2 other FDCs available	Yes 5 other INNs of FDCs are	Yes	Yes 4 other FDCs	Yes 4 other FDCs
Anti TB Medicines							
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	No	No	No	No	Yes	No	No
ethambutol + isoniazid + pyrazinamide + rifampicin	No	Yes	Yes	No	Yes	No	Yes
ethambutol + isoniazid + rifampicin	No	Yes	No	No	Yes	No	Yes
isoniazid + pyrazinamide + rifampicin	No	Yes	Yes	No	Yes	No	Yes
isoniazid + rifampicin	No	Yes	Yes	No	Yes	Yes	Yes
Antimalarial medicines including prevention							
artemether + lumefantrine	No	Yes	Yes	No	Yes	No	Yes
artesunate + amodiaquine	No	Yes	No	No	Yes	No	Yes
artesunate + mefloquine	No	No	Yes	No	No	No	No
artesunate + pyronaridine tetraphosphate	No	No	No	No	No	No	No
dihydroartemisinin + piperaquine phosphate	No	No	No	No	Yes	No	Yes
sulfadoxine + pyrimethamine	No	Yes	No	No	Yes	No	Yes
Non-communicable diseases							
Cardiovascular – Hypertension, etc							
lisinopril + amlodipine	No	No	No	Yes	No	Yes	No
lisinopril + hydrochlorothiazide	No	Yes	No	Yes	No	No	No
telmisartan + amlodipine	No	Yes	No	Yes	No	Yes	No
telmisartan + hydrochlorothiazide	Yes	Yes 12 other FDCs	No	Yes 24 INNs of FDCs are available	No	No 26 other FDCs	No 2 other FDCs
Diabetes							
None	No	1 FDC available	No	10 INNs of FDCs are available		9 FDCs available	No
Respiratory							
budesonide + formoterol	Yes Other FDCs also reimbursed	Yes 1 other FDC	Yes	Yes 10 other FDCs are available	No	Yes 10 other FDCs	Yes 1 other FDC
Pain							
None	No	1 FDC available	No	No	5 other FDCs available	No	No

	Iran	Kenya	Kosovo	Latvia	Nigeria	Romania
Infectious diseases						
Antibiotics (Prevention malaria, etc)						
sulfamethoxazole + trimethoprim	Yes	Yes	Yes	Yes	Yes	Yes
HIV FDCs						
abacavir + lamivudine	No	Yes	Yes	Yes	No	Yes
dolutegravir + lamivudine + tenofovir	No	Yes	No	No	No	No
efavirenz + emtricitabine + tenofovir	Yes	No	Yes	Yes	No	Yes
efavirenz + lamivudine + tenofovir	No	Yes	No	No	No	No
emtricitabine + tenofovir	Yes	Yes	Yes	Yes	No	Yes
lamivudine + nevirapine + zidovudine	No	Yes	No	No	Yes	No
lamivudine + zidovudine	Yes 10 other FDCs	Yes	Yes	Yes	Yes	Yes 5 other FDCs
Anti TB Medicines						
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	No	No	No	No	No	No
ethambutol + isoniazid + pyrazinamide + rifampicin	Yes	Yes	No	No	No	Yes
ethambutol + isoniazid + rifampicin	Yes	Yes	No	No	No	No

(*Continued*)

Table 2. (Continued).

	Iran	Kenya	Kosovo	Latvia	Nigeria	Romania
isoniazid + pyrazinamide + rifampicin	Yes	Yes	No	No	No	Yes
isoniazid + rifampicin	Yes 4 other FDCs	Yes	Yes	No	Yes	Yes 1 other FDC
Antimalarial medicines including prevention						
artemether + lumefantrine	Yes	Yes	No	No	Yes	No
artesunate + amodiaquine	No	No	No	No	Yes	No
artesunate + mefloquine	No	No	No	No	No	No
artesunate + pyronaridine tetraphosphate	No	No	No	No	No	No
dihydroartemisinin + piperaquine phosphate	No	Yes	No	No	No	No
sulfadoxine + pyrimethamine	Yes 7 other FDCs	Yes	No	No	Yes 1 other FDC	No 1 other FDC
Non-communicable diseases						
Cardiovascular – Hypertension, etc						
lisinopril + amlodipine	No	No	No	Yes	No	No
lisinopril + hydrochlorothiazide	Yes	No	No	No	No	No
telmisartan + amlodipine	No	No	No	Yes	No	No
telmisartan + hydrochlorothiazide	No 10 other FDCs	No	No	Yes	No 2 other FDCs	Yes 22 other FDCs
Diabetes						
None	5 FDCs available	No	No	No	No	7 FDCs available
Respiratory						
budesonide + formoterol	Yes 23 other FDCs	Yes	Yes	Yes	No	Yes 5 other FDCs
Pain						
None	No	No	No	No	No	1 FDC available

	South Africa	Srpska	Sudan	Vietnam	Zambia	Zimbabwe
Infectious diseases						
Antibiotics (Prevention malaria, etc)						
sulfamethoxazole + trimethoprim	Yes	Yes	Yes	Yes	Yes	Yes
HIV FDCs						
abacavir + lamivudine	Yes	Yes	No	No	Yes	Yes
dolutegravir + lamivudine + tenofovir	Yes	No	No	No	Yes	Yes
efavirenz + emtricitabine + tenofovir	Yes	No	No	No	Yes	Yes
efavirenz + lamivudine + tenofovir	No	No	No	Yes	Yes	Yes
emtricitabine + tenofovir	Yes	Yes	No	No	Yes	Yes
lamivudine + nevirapine + zidovudine	No	No	No	Yes	Yes	Yes
lamivudine + zidovudine	Yes 2 other FDCs	Yes 1 other FDC	No	Yes 2 other FDCs	Yes 1 other FDC	Yes
Anti TB Medicines						
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	No	No	No	No	No	No
ethambutol + isoniazid + pyrazinamide + rifampicin	Yes	Yes	Yes	Yes	Yes	Yes
ethambutol + isoniazid + rifampicin	No	Yes	Yes	Yes	Yes	Yes
isoniazid + pyrazinamide + rifampicin	Yes	No	Yes	Yes	Yes	Yes
isoniazid + rifampicin	Yes	Yes	Yes	Yes 1 other FDC	Yes 1 other FDC	Yes
Antimalarial medicines including prevention						
artemether + lumefantrine	Yes	No	Yes	Yes	Yes	Yes
artesunate + amodiaquine	No	No	No	Yes	No	Yes
artesunate + mefloquine	No	No	No	Yes	No	No
artesunate + pyronaridine tetraphosphate	No	No	No	No	No	No
dihydroartemisinin + piperaquine phosphate	No	No	No	Yes	No	No
sulfadoxine + pyrimethamine	No	No	No 2 other FDCs	Yes	Yes	Yes
Non-communicable diseases						
Cardiovascular – Hypertension, etc						
lisinopril + amlodipine	Yes	No	No	Yes	No	No
lisinopril + hydrochlorothiazide	Yes	Yes	No	Yes	No	No
telmisartan + amlodipine	Yes	No	No	Yes	No	Yes
telmisartan + hydrochlorothiazide	Yes 17 other FDCs	No 7 other FDCs	No 1 other FDC	Yes 16 other FDCs	Yes 2 other FDCs	Yes 5 other FDCs
Diabetes						
None	2 FDCs available	7 FDCs available	NA	7 FDCs available	No	1 FDC available
Respiratory						
budesonide + formoterol	Yes 2 other FDCs	Yes 4 other FDCs	Yes 1 other FDC	Yes 5 other FDCs	No	No
Pain						
None	3 FDCs available	No	No	15 FDCs available	No	No

FDC, Fixed dose combination; HIV, Human immunodeficiency virus; INN, International non-proprietary name; TB, tuberculosis

Table 3. Positive clinical and economic (general) considerations associated with FDCs.

Clinical benefits associated with FDCs (general)	Economic benefits (general) associated with FDCs
• Simplifies the treatment schedule – which can be particularly important in LMICs where there are low literacy levels as seen in a number of sub-Saharan African countries • Easier to prescribe • Improved adherence with reduced pill burden • Minimal frequency of medicine consumption and reduced chances of patients missing doses • Potential to attain clinical goals more rapidly through complimentary additive effects of the components and/or reduced titration times • Potential for increased tolerability and/or fewer side-effects through the combination of synergistic medicines • Reduced chances of stockouts with FDCs versus the components especially for FDCs containing multiple medicines; consequently, potentially improving clinical outcomes	• Potential for reduced overall costs enhanced by synergism with lower doses – potential for lower costs than the components enhanced if FDCs are produced and procured at low cost aided by mass approaches to production, packaging, and distribution • Reduced space for storage and distribution/potentially reduced logistical costs • Potential for improved shelf life • Now seeing in countries that prices of FDCs cannot be higher than the costs of the individual components (e.g. Slovenia) and may even be lower (e.g. India and Zambia)

FDC, Fixed dose combination; HIV, Human immunodeficiency virus; INN, International non-proprietary name; TB, tuberculosis

Table 4. Positive clinical considerations with FDCs across disease areas.

Disease area	Benefits of FDCs
Cardiovascular diseases including hypertension	• Improved dose frequency and ease of administration help improve adherence especially where patients are on multiple medicines due to existing co-morbidities – potentially improving disease management • Potential for improved effectiveness by combining different treatments with different mechanisms of action, e.g. different lipid-lowering treatments • One component of an FDC may offset the side-effects seen with other components, e.g. ACE inhibitors offsetting one of the major side effects associated with calcium channel blockers • Potential for minimal adverse effects alongside improvement in disease management • Improved long-term adherence through reduced pill burden especially important among aging populations, e.g. European LMICs
Type 2 Diabetes Mellitus (T2DM)	• Potential for improved adherence through reduced pill burden – especially important in T2DM patients with multiple co-morbidities to enhance adherence rates • Improved disease control for patients with T2DM as well as potentially reducing complications through using medicines with different mechanisms of action • In some countries, helps increase the prescribing of metformin where this is a concern and SUs available in combination with metformin
Respiratory diseases	• FDCs containing ICS/LABAs are seen as a standard of care for the maintenance of patients with asthma • Improved acceptance of FDCs versus separate inhalers helped by easier administration • Reduced doses of steroids where there are concerns with continued high doses of steroids for maintenance among patients with asthma • FDCs seen to improve the quality of life of patients with asthma through improved adherence and better maintenance of disease targets
Pain	• Improved potential for pain management with FDCs with different mechanisms of action where concerns with abuse or increased side-effects if the dose of one component is increased to manage the pain • Multiple mechanisms for a broader effect
Malaria	• Improved effectiveness and treatment success • Improved adherence to prescribed medicines enhanced by the potential for shortened duration of treatment • Potential for decreased resistance using medicines with different mechanisms of action • Potential for reduced costs
Tuberculosis (TB)	• FDCs may help prevent the emergence of resistant strains especially given the length and complexity of the treatment regimens involved • Increased effectiveness against resistant cases with medicines with different mechanisms of action • Reduces the incidence of MDR-TB • Synergism at lower doses • Complex treatment regimen eased by FDCs thereby enhancing completion rates • Dispersible FDCs for children easing administration
Human immunodeficiency virus (HIV)	• FDCs containing medicines with different mechanisms of action typically improves treatment outcomes • Synergism at lower doses • FDCs may help prevent the emergence of resistant strains • Increased effectiveness against resistant cases • Combining tablets simplifies treatment regimens and standardizes doses prescribed aiding subsequent quality of care • Patients are unable to default on specific medicines believed to be causing side-effects such as dizziness and drowsiness seen with efavirenz

ACE, angiotensin-converting enzyme; FDC, Fixed Dose Combination; ICS/LABAs, Inhaled corticosteroids/long-acting β agonists; MDR-TB, Multidrug resistant TB; SU = sulfonyl urea.

Table 5. General concerns regarding FDC.

Clinical concerns associated with FDCs (general)	Economic concerns (general) associated with FDCs
• Reduces the ability to titrate individual doses to the specific needs of patients • Potential for overtreatment if physicians and patients are not fully aware of the constituents of FDCs – especially important if patients are switched to different FDCs • FDCs can increase polypharmacy especially in patients with chronic NCDs • Issues of pharmacokinetics in some FDCs including issues of dissolution, absorption and drug:drug interactions • Missing doses of an FDC has a greater impact than missing doses of one of the medicines in the FDC • Challenging to ascertain responsible medicine for ADRs – especially important for pharmacovigilance	• Potentially appreciably higher prices for the FDC versus the cost of the components combined • Typically only available as 'branded' medicines in some countries and consequently only available in private pharmacies rather than public facilities and not in rural areas, e.g. Cameroon

ADRs, Adverse Drug Reactions; FDC, Fixed Dose Combination

Table 6. Clinical concerns regarding FDCs across disease areas.

Disease area	Concerns with FDCs
Cardio Vascular (CV) diseases including hypertension	• Reduces the ability to tailor treatment to individual patients especially where adverse effects are seen with the prescribed FDC • More limited options with FDCs versus individual components • More difficult to adjust doses when needed potentially enhancing treatment inertia • Potential for doubling doses of medicines if patients and prescribers are not fully aware of the constituents of prescribed FDCs • Clinical rationality of a number of CV FDCs with the potential for inadequate dosing and increasing costs • Concerns with the bioequivalence and pharmacokinetics of some FDCs for CV diseases
Type 2 Diabetes Mellitus (T2DM	• More difficult to adjust doses thereby potentially reducing the ability to tailor treatment to individual patients • More limited options with FDCs versus individual components • Reduced positive effect of metformin on CV events with reduced doses of metformin or with metformin/sulfonyl urea combinations • Potential for doubling doses of medicines if patients and prescribers are not fully aware of the constituents of prescribed FDCs • Clinical rationality of a number of FDCs, e.g. metformin FDCs in India • FDCs enhance the potential for polypharmacy, e.g. in Slovenia many patients with T2DM are typically on 4 or more INN medicines which was not often seen before the availability of FDCs
Respiratory diseases	• Reduces the potential for effective management especially where there are concerns with the doses of steroids administered – as a result, potential for over medication with steroids • Patients may need to use different inhaler devices with different FDCs impacting on adherence in practice • Increasing concerns with prescribing of LABA/ICS combinations in patients with COPD unless asthma-like symptoms
Pain	• Reduces the ability to tailor treatment to individual patients • More difficult to adjust doses • Potential for substance misuse if currently taking FDCs due to the subjective nature of pain • Limited clinical justification for FDCs to treat pain among some of the coauthors • Potential to enhance irrational prescribing
Malaria	• Potential concerns with tolerance to mefloquine FDCs • Appreciable number of unapproved FDCs in some LMICs • Concerns with the pharmacokinetic profile of some FDCs for malaria impacting on their effectiveness and safety • Potential loss of effectiveness • Potential development of drug resistance to one or more of the components leading to loss of therapeutic options
Tuberculosis (TB)	• Difficult to desensitize patients in the event of adverse effects • Potential for increased adverse events • Some constituents of FDCs may cause more adverse effects than the originators • Potential quality issues when medicines are combined especially with rifampicin in FDCs for TB – consequently vigilance is needed to monitor the quality of rifampicin as a key component of antimalarial FDCs given concerns with certain rifampicin FDCs in countries such as South Africa • Potential loss of effectiveness • Potential development of drug resistance to one or more of the components leading to loss of therapeutic options • The interaction between efavirenz as well as lopinavir, dolutegravir, raltegravir with bedaquiline is a problem for patients with HIV who also have MDR-TB (especially in sub-Saharan Africa) – necessitating a switch to twice daily nevirapine with separate companion tablets – antiretroviral FDCs without bedaquiline drug interactions are strongly recommended in these patients
Human immunodeficiency virus (HIV)	• Difficult to desensitize patients in the event of adverse effects, with the potential for increased adverse events with FDCs • Some constituents of FDCs may cause more adverse effects than the originators necessitating careful monitoring of patients • Potential loss of effectiveness over time • Potential development of drug resistance to one or more of the components leading to loss of therapeutic options • Currently, no liquid formulation FDCs are available for pediatric patients • Imperative to educate patients that FDCs cannot be crushed or dissolved to improve swallowing as bioequivalence will be compromised • Supply chain integrity is imperative to ensure a continuous supply of ARV FDCs for patients with interruptions in supply associated with sub-clinical outcomes

CV, cardiovascular; FDC,Fixed Dose Combination; ICS/LABAs,Inhaled corticosteroids/long-acting β agonists; INN, International non-proprietary name; MDR-TB, Multidrug-resistant TB.

BOX 1. Potential initiatives that can be undertaken by key stakeholder groups to enhance the availability and prescribing of valued FDCs.

A) Clinical and other considerations

- Emphasize the importance of adherence to treatments especially for patients with chronic NCDs and how valued FDCs can help with this. Concurrent with this, improve prescriber education about the benefits of valued FDCs starting in medical school and continuing post qualification – similarly for pharmacists who are increasingly involved with patient education regarding their medicines and the importance of adherence to prescribed doses
- Possibly linked to this, the development of quality prescribing indicators potentially linked with financial rewards
- Pharmaceutical companies to provide robust clinical trial data demonstrating improved outcomes and adherence with FDCs versus the components separately to aid listing in country/region reimbursement list/EML (such data when available can be incorporated into robust health technology assessments of new FDCs)
- Investigate further the clinically meaningful benefits of the polypill especially for sub-Saharan Africa given the appreciable increase in morbidity and mortality due to CV diseases in recent years in these countries
- Robustly considering any potential drug:drug interactions or increased adverse effects in patients with HIV subsequently developing chronic NCDs (increasingly happening in sub-Saharan Africa) and prescribed FDCs – especially as this co-morbid population is likely to experience challenges with medication adherence/polypharmacy
- The process from transitioning from individual medicines to FDCs should be carefully managed in terms of supply chain management (where problems currently exist) to facilitate procurement at a central level (and hence procurement at lower prices) and subsequent distribution
- Appropriate patient counseling also needs to take place to optimize the process – with intensive adherence counseling still needed especially among patients with limited education. In view of this, if appropriate create policies that enhance capacity within health-care systems that help spread correct information and awareness regarding the value and effectiveness of pertinent FDCs as well as use patient organizations where these exist to spread key messages – this can include instigating educational activities among physicians and pharmacists in medical and pharmacy schools and post-qualification
- Accelerating the registration/pricing procedures for valued FDCs in countries where this is a concern, e.g. Sudan. This can be addressed through the provision of scientifically sound guidelines and robust data supporting their registration as well as a review of reimbursement/pricing procedures where there are concerns
- More flexible approaches to private pharmacies regarding the availability of FDCs especially in rural areas where this is a concern, e.g. Cameroon

B) Economic

- Realistic pricing expectations and considerations especially where there are high patient co-payments or strict pricing regulations, e.g. Estonia, to help overcome concerns with the over-pricing of FDCs and enhance their chances of being reimbursed/listed in national/regional EMLs – typically initially robust health technology assessments using cost minimization approaches are needed among LMICs to enhance their listing in national EMLs (progressing to cost-effectiveness analyses as sophistication levels grow)
- Addressing issues of affordability and access where these exist – including reducing additional patient co-payments for the FDC versus multiple tablets of the same medicines where these exist especially for valued FDCs, e.g. Bulgaria and Poland
- Concurrent with this, promoting local pharmaceutical company participation in the manufacturing of FDCs to agreed quality standards through incentives and other mechanisms to help address supply chain and affordability/access issues where these exist

Abbreviations: EML = Essential Medicine List; FDC = Fixed Dose Combination; LMICs = Lower- and Middle-Income countries; NCDs = Non-communicable diseases

BOX 2. Potential initiatives that can be undertaken by key stakeholder groups to reduce or negate the availability of FDCs where concerns.

A) Clinical

- The development of public/private partnerships to help standardize treatment approaches including the prescribing of FDCs
- Provision of robust health technology assessments to support listing/funding of FDCs in LMICs – especially for more elderly patients with high pill burdens. This includes robust cost-effectiveness analyses across LMICs demonstrating their value versus the prescribing of multiple medicines for the same patient population
- Concomitant with this – greater focus on issues of potential polypharmacy with FDCs especially in elderly patients with multiple co-morbidities
- Only register FDCs of proven clinical value, enforced through tighter regulations – especially important in countries with existing high rates of irrational FDCs, e.g. India – although changing – and to prevent the future availability of FDCs where concerns
- Improved education of undergraduates and physicians where concerns with irrational FDCs, e.g. India. This should be continued with activities after qualification including in-service training/continual professional development to enhance adherence rates among patients to prescribed FDCs given ongoing concerns with long-term adherence to medicines especially in patients with chronic asymptomatic conditions
- Improve pharmacovigilance activities especially for FDCs where there are safety as well as drug:drug interaction concerns
- Greater interaction and empowerment of national patient organizations to enhance the appropriate use of valued FDCs and limit the prescribing/use of FDCs where there are clinical and other concerns
- Enforce legislation and monitor activities to reduce or negate non-prescription sales of FDCs especially where concerns with their rationality

B) Economic

- Tougher hurdles for pricing/reimbursement considerations to reduce reimbursement/listing of FDCs of limited clinical value as well as unjustifiably higher prices than the components combined

FDC = Fixed Dose Combination; LMICs = Lower- and Middle-Income countries

include in this perspective paper as well as help with contextualization of the findings. This especially given the paucity of health economic studies of FDCs in LMICs versus high-income countries.

We are also aware that we did not include all LMICs. However, we did include LMICs from across continents to help address this. Overall, we believe our findings and suggestions are robust providing direction for the future.

3. Conclusions

FDCs are valued across a range of disease areas as seen by the number of FDCs listed in WHO and country EMLs (Table 2). This reflects their value with improving disease management, reducing adverse reactions and improving adherence rates. This is despite only a limited number of pharmacoeconomic analyses to date in high priority disease areas in LMICs versus

high-income countries to fully appraise whether FDCs are pharmacoeconomically justified. Having said this, there are a number of concerns with FDCs including increasing the number of adverse reactions, reducing effectiveness in routine clinical practice, encouraging imprecise diagnoses and increasing costs which affect their overall value. Consequently, their availability and use need to be carefully managed in routine clinical care, with the use of FDCs enhanced by the availability of robust clinical and economic data. A number of activities are also needed to enhance their utility alongside more pharmacoeconomic analyses. These include greater education of physicians and patients of their value where pertinent alongside activities to further improve adherence rates especially in patients with chronic diseases. Concurrent with this, ongoing activities including stricter regulations to limit the availability and use of FDCs of limited value.

Overall, we are likely to see greater availability and use of valued FDCs across LMICs in the future to improve patient care as more evidence becomes available. This is especially important in patients with infectious diseases such as HIV and TB as well as NCDs including CV diseases and diabetes.

4. Expert opinion

We expect to see growing availability and use of FDCs in both infectious and non-infectious disease areas in the future building on their potential advantages. Advantages include improved response rates when combined especially where there are side-effect concerns at optimal doses of single agents. In addition, improved adherence rates through more simplified dosing regimens. Improved adherence rates are particularly important where there are complex treatment regimens and where patients are often on multiple medicines to help control their disease. These advantages are recognized by the endorsement of FDCs in priority disease areas by the WHO as well as by national and regional governments in their lists of medicines available within public health-care systems. FDCs can also be cost-effective; however, there is a paucity of such data within LMICs.

There are though recognized disadvantages with FDCs. These include the availability of irrational FDCs especially in countries such as India and Nepal, although this is changing. There are also concerns that the pharmacogenetics of patients will not be taken into consideration in their development, concerns with identifying which component is responsible for side-effects when these occur, challenges with dose adjustments and appreciable higher prices for the FDCs versus the separate components. Higher prices can persist when the components are available as lower-cost generics but the FDC prolongs the patent life. Concerns with dose adjustments can be helped by making multiple dosing forms available. We are likely to see an increasing number of studies conducted in LMICs demonstrating the clinical and economic advantages of FDCs to address such concerns. This will be helped by the growing capability of LMICs to conduct robust health technology assessments especially middle-income countries. The listing of FDCs within reimbursement and procurement lists will also be helped by realistic pricing versus the components separately. Pricing is particularly important where there are high patient co-payments. We are also likely to see improved regulatory standards to remove or negate marketing authorization of FDCs of limited value, or unapproved FDCs, building on previous initiatives in Europe via the EMA and in the US via the FDA. This is already happening in India leading to the removal of over 300 FDCs in recent years.

We are also likely to see educational initiatives to improve the knowledge of FDCs among physicians, pharmacists, and patients. This includes addressing concerns with over treatment if physicians and patients are not fully aware of the components of FDCs as well as helping with the transition from individual medicines to FDCs where necessary especially for patients with NCDs. Such activities are likely to be increasingly combined with initiatives to enhance adherence rates to prescribed medicines including educational activities and adherence clubs to further improve patient care especially in patients with asymptomatic chronic conditions. Consequently, as mentioned, we are likely to see growing utilization of valued FDCs across LMICs in the future especially with LMICs striving to achieve their SDGs. Alongside this, an increasing number of publications undertaken in LMICs demonstrating that FDCs are pharmacoeconomically sound within a number of disease areas although there will continue to be concerns with some of them.

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