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## Chapter 22 Phase IV studies

### 1. Introduction to Phase IV studies

The main focus of this book is on randomized controlled field trials of health interventions in LMICs, many of which can be classified as Phase III trials (see Chapter 2, Section 3). This chapter gives a brief overview of Phase IV studies that are often carried out after an intervention has been shown to be efficacious in Phase III trials. We give a brief description of the rationale and some of the terminology used in such studies, outline the main types of Phase IV study, discuss some key issues in the design of such studies, and give a brief description of two specific Phase IV studies.

For new drugs or vaccines, the evidence from one or more Phase III trials, taken together with the results of the Phase I and II trials, will be presented to licensing authorities to register the product for clinical or public health use. However, the total number of participants included in Phase I to III trials of a new product will often be no more than a few thousand, and there are usually important public health issues that will have been incompletely addressed at the time a product is licensed. For example, individuals included in Phase III trials will often have been a carefully selected sample of the population and will not include all of those eligible for eventual administration of the product. Particular groups may have been excluded, such as children and adolescents, the very undernourished, or pregnant women, but these groups will often receive the product when it is in general use, and it is important to collect data on both the safety and the effectiveness of the product in these groups. Also, in most Phase III trials, great care will have been taken with product supply and storage, and, if the dosing regimen requires multiple doses, care will have been taken to ensure that the interval between doses was as recommended. Rigid adherence to such intervals is much less likely once the product is in general use. For these reasons, it will be important to measure whether the effect of the product, when it is administered in a routine health system or programme, is similar to the efficacy that was assessed in the Phase III trials conducted in a research setting. Phase IV studies are conducted to assess the *effectiveness* of an intervention when it is in public health use, as compared to the *efficacy* of the intervention as assessed in a carefully controlled Phase III trial (see Section 2.1).

Most Phase III trials will not have been large enough to detect reliably important, but relatively uncommon, side effects. For example, a serious adverse effect (SAE) of an intervention that occurs, on average, in one in every 2000 recipients may well be missed in a Phase III trial that involved only a few thousand participants. There may also be other unexpected effects when an intervention is implemented in a public health programme that were not apparent in the carefully controlled situation of a Phase III trial. For example, in a trial of a health education intervention in schools, teachers may be willing to promote condom use when they have been carefully trained, supported, and supervised, as part of the trial procedures. However, when the intervention is implemented on a widespread basis, in settings where condom use is unpopular and talking of such things with young people frowned upon, teachers might actually discourage use without the support that was included in the trial. It is important that studies are conducted to detect such adverse effects once an intervention is in routine use. Whenever possible, such Phase IV studies should be used as the basis for developing systems that persist after the study, so that routine health systems can continue to detect such events.

Historically, assessment of how interventions work in ‘real-world’ public health programmes has been relatively neglected. However, presently, such Phase IV research is receiving increasing attention. It encompasses post-marketing surveillance of the effect of interventions and implementation research which investigates better ways of ensuring the successful delivery of an intervention (such as how to increase the coverage of a vaccination programme). A common goal of Phase IV studies is to provide evidence that the health intervention can be successfully and safely integrated into public health or clinical practice where ‘successful’ means that it is not only feasible to do so, but also that the intervention remains effective and its implementation is not associated with any serious adverse effects.

This chapter focuses mainly on Phase IV studies related to the introduction of new drugs or vaccines, but similar studies can be used to evaluate other types of health intervention such as surgical procedures, health education, or peer supporters to encourage adherence to treatment regimens.

Phase IV research serves three major functions:

1. to support pharmacovigilance systems in monitoring the safety of new interventions used in large populations and in specific groups who were not studied adequately in the pre-marketing phases such as children, pregnant women, the elderly, or those with co-morbidities
2. to determine the effectiveness of an intervention in a routine health system, as opposed to within a carefully controlled trial
3. to assess new strategies of use of approved products or interventions, such as the evaluation of anti-malarials when used for intermittent presumptive treatment, rather than either for malaria prophylaxis or for treatment of a diagnosed malarial infection.

Furthermore, studies to seek ways of widening the coverage, ensuring a more equitable distribution or conducting an economic evaluation of an intervention (see Chapter 19) may also be encompassed by Phase IV studies. A key issue with respect to such studies is that they are conducted after a product has been licensed or is already in widespread use. Thus, placebo-controlled trials are generally ruled out for ethical reasons, and observational designs are often employed. A full description of all the potential observational study designs is beyond the scope of this chapter. However, because of the importance of Phase IV studies and the overlap with many of the field research issues covered in this book, after defining some of the key terms and concepts, Section 2 of this chapter gives a brief overview of some of the commonest Phase IV research approaches.

### 1.1. Efficacy and effectiveness

A distinction should be made between the effect of the intervention, as measured in a Phase III trial, called the *efficacy* of the intervention, and the effect of the intervention when it is delivered in a public health programme, called the *effectiveness* of the intervention. Generally, it is expected that the efficacy of an intervention will be greater than its effectiveness, for the reasons outlined in Section 1. However, this is not always the case. For example, when some vaccines are administered to large populations, there are at least two factors that may operate to reduce the incidence of disease. First, the vaccine may offer individual protection to recipients of the vaccine. Second, the reduction in the number of individuals who acquire the disease as a consequence of vaccination may reduce the overall level of infection in the community, and thus even those who are unvaccinated may be at lower risk of acquiring disease, simply because they are less likely to be exposed to someone with the infection. Such *herd effects* may be substantial for some person-to-person infections, for which humans are the main reservoir. If the vaccine coverage is high enough, the effectiveness of the vaccine may be higher than would have been predicted from Phase III efficacy trials, in which typically, at most, half of the eligible population is vaccinated. [Fine et al. \(2011\)](#) give an overview of herd effects.

The overall impact of an intervention against a disease in a population, sometimes known as the *community effectiveness* or *system effectiveness* of the intervention, will depend on the *effectiveness* of the intervention and its *effective coverage*, i.e. the proportion of the *target* population who receive it. The *target* population consists of all those who should receive (would benefit from receiving) the intervention. An example of how an evaluation of the effective coverage of a broad range of different health services was used to benchmark the performance of the health system in the various states of Mexico is given in [Lozano et al. \(2006\)](#).

### 1.2. Stakeholders

The primary audience for Phase IV studies is health policy decision makers, but other stakeholders may include regulatory agencies, industry, health care professionals, patients, community groups, media, and suppliers. Regulatory agencies and public health officials will seek to ensure the continuous evaluation of an intervention's risks and benefits. Industry engages in Phase IV research to determine the effects of long-term use, as requested or demanded by regulatory agencies, but also to inform key strategic and operational decisions related to the marketing of their products. Governments, decision makers, and policy makers need high-quality evidence on effectiveness and cost-effectiveness in the real world, as well as in Phase III trial settings, in order to design and implement public health programmes that optimize health gains and reduce health inequity. For clinicians, Phase IV study data can guide their prescribing and the advice they give to their patients.

## 2. Types of Phase IV study

## 2.1. Safety/pharmacovigilance

Pharmacovigilance is defined as ‘the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems’ (World Health Organization, 2006). Pharmacovigilance studies are designed to detect and assess both long-term and short-term adverse effects of medicines (including drugs and vaccines). Regulatory agencies will often require that specific monitoring is conducted after a product is licensed (post-marketing safety monitoring or pharmacovigilance) that is designed to detect the occurrence of rare, but serious, adverse effects of the product. Similar issues apply to medical devices and prostheses.

Pharmacovigilance studies can include observational or intervention studies. Common designs include case-control studies, cohort studies (cohort event monitoring), and spontaneous (passive) reporting schemes. In some circumstances, RCTs might also be possible. The main method used in HICs is the collation of adverse drug reaction reports submitted by clinicians, which are compiled and analysed by national pharmacovigilance centres. The reports may also be submitted to the WHO Programme for International Drug Monitoring (<<http://www.who-umc.org>>). However, this reporting system is not yet functional in most LMICs, and, even in HICs, the system is acknowledged to be an imperfect way to detect all of the adverse events (AEs) that might be associated with a particular product. However, monitoring for product safety is particularly important in LMICs, often with their overburdened health care systems and frequent polypharmacy. Other potential safety issues in LMICs include the widespread manufacture and sale of counterfeit, substandard, or expired medicines, and potentially unsafe drug donation practices. An example of how pharmacovigilance can be built into a broader Phase IV study is given in Section 4.1.

## 2.2. Intervention effectiveness

As discussed in Section 1, the effectiveness of an intervention may well be different in the complex and dynamic situation of a routine health system, compared to the context of a carefully controlled Phase III trial. Effectiveness studies evaluate the impact of an intervention when delivered under real-world conditions in a routine health system. Such studies are especially important when a new intervention is first introduced into a public health programme. The decision to introduce the intervention will usually be based upon the results of one or more Phase III trials, including a cost-effectiveness analysis, often using data derived from the Phase III trials. However, it is important to evaluate both the effectiveness and cost of the intervention, as used in the public health programme, and this will generally require the setting up of specific studies. For example, a series of such studies were conducted when rotavirus vaccines were introduced into public health use (Patel et al., 2011).

Phase IV studies may also be appropriate for interventions which are relatively well established in a public health programme. These may be drugs or vaccines that have been in use for a number of years already, or other interventions which may have been implemented with or without preceding efficacy trials or for which the effectiveness of the intervention is unknown, even if the efficacy had been established in controlled intervention trials. For example, controlled trials were conducted to measure the impact of introducing insecticide-treated bed-nets (ITNs) as a measure to reduce deaths from malaria in malaria-endemic areas. These showed that this intervention had a substantial impact on child mortality. A Phase IV study to evaluate the impact of such bed-nets, when implemented in a public health programme, was conducted by Schellenberg et al. (2001). In this study, a programme was rolled out across two rural districts of southern Tanzania over a 2-year period, in which subsidized ITNs were made available at shops and kiosks. The proportion of young children who slept under an ITN was estimated through population-based surveys, and the impact on child mortality monitored through a case-control study, in which the prior use of an ITN was compared among children who had died from malaria and those who survived. All child deaths were identified within a demographic surveillance area. This Phase IV study confirmed that ITNs had a major impact on child mortality within a routine programme, and the study also elucidated ways in which that impact might be increased by modifications to the programme delivery system.

Phase IV studies of health system effectiveness are designed to understand reasons for the decay of the impact of an intervention that results from individual and system behaviour, including access to the intervention, diagnostic targeting, provider compliance, and patient adherence. Figure 22.1 summarizes the outcome of Phase IV studies conducted in Tanzania to determine why highly efficacious anti-malarial treatments had low community effectiveness. Controlled trials had shown that artemisinin combination treatments (ACTs) have very high efficacy for the treatment of uncomplicated malaria, with roughly 98% of patients who received treatment within carefully conducted efficacy trials cured. A community-based survey found that only 60% of those with malaria sought care from a clinic that had ACTs. Studies within the clinics showed that 95% of those who came to these clinics had an appropriate diagnostic

test performed, and, in 95% of those diagnosed with malaria, the correct treatment was prescribed. Further studies in the patients who were given the correct prescription of ACT showed that only 70% of them adhered correctly to the treatment as prescribed. Taken together, this series of Phase IV studies showed that less than 40% of people with uncomplicated malaria in the community were effectively treated, despite ACTs, which had a 98% efficacy, being made available. Such Phase IV studies can not only document and measure the failings in the health system, but they can also be used to investigate the reasons behind these problems and the potential actions that can be taken to fix them (see Section 4.1).

Figure 22.1 represents what happened in the catchment population as a whole, but it is important, in such studies, to measure system effectiveness by socio-economic status, and among specific vulnerable groups, as this may reveal substantial heterogeneity in the findings, according to these factors.

### 3. The conduct of Phase IV studies

Phase IV studies should follow the general guidelines, as described elsewhere in this book, with respect to the selection of the study population and study design, sample size calculations, ethics clearance and consideration of other governance issues, and the training and supervision of study staff.

#### 3.1. Design issues

There are multiple observational designs and evaluation schemes that can be used in Phase IV studies to assess the effectiveness, cost-effectiveness, and safety of an intervention in real-world settings. Details of these approaches is beyond the scope of this book, but the use of non-randomized study designs to evaluate interventions is discussed in [Victora et al. \(2004\)](#) and [Bonell et al. \(2011\)](#).

#### 3.2. Study sites

Whereas Phase I to III trials are often restricted to relatively small-scale research settings with good infrastructure, Phase IV studies are typically conducted over wider areas where health care and the intervention in question are delivered through routine health systems. A variety of service providers may be involved, including public, private-for-profit, private-not-for-profit, and community-based providers. A way of encompassing this complexity is to use the district as the unit of implementation and analysis within Phase IV studies. In many countries, districts are the core administrative unit for governmental health and other programmes, and the smallest unit that includes all the major features of the health system, from a hospital down to community health workers. They are usually the lowest unit that plans and allocates budgets, manages training, and aggregates health information. They are easily identifiable and often have some level of sociocultural and economic homogeneity. Wherever possible, Phase IV studies should support and strengthen existing health systems, rather than setting up special structures that may weaken the health system in the long term.

One of the challenges in conducting Phase IV studies in these situations is to balance the need to study the intervention in a real-world setting with the need to be able to collect reliable data. Health and demographic surveillance sites (HDSS) longitudinally monitor and register the total population living within a geographically defined area. They collect a broad array of important health-related parameters at the household and individual levels, including pregnancies, births, deaths, causes of death, socio-economic status, care-seeking behaviour, and immunization status. HDSS sometimes cover whole districts, with populations of 50 000 to more than 100 000 people, and therefore include the full range of health service providers. HDSS are increasingly being used for Phase IV studies of effectiveness and safety (see Section 4.1). Effectiveness studies involving HDSS can measure the effectiveness of the system in delivering the intervention to the whole community, as well as the effectiveness of the delivered intervention in affecting individual health status. The large numbers of exposures to the intervention that can be monitored longitudinally in HDSS make them useful for pharmacovigilance studies. The research infrastructure associated with HDSS also makes it possible to interpret results contextually and to estimate cost-effectiveness. The longitudinal history available on all residents in an HDSS provides data that makes HDSS highly valuable partners in effectiveness trials and Phase IV studies.

#### 3.3. Ethics and governance

Planners of Phase IV studies are confronted with the need to maintain sufficient oversight of intervention delivery to ensure that the approach is as planned, while simultaneously allowing for realistic adaptation and tailoring by

providers. Governance of such studies needs a balance between the requirements of routine health systems and international scientific standards. It is valuable to have a separate committee that involves donors, governments, regulators, industry, and key stakeholders who discuss the approaches used and to offer guidance as to their selection, interpretation, and use of results. Also see Chapters 6, 7, and 9.

Phase IV studies, in which any new data on people are collected, generally need ethical clearance from the relevant national and institutional bodies. Such studies pose some specific challenges, in terms of ethical considerations, as they may involve comparison of new vs old technology and expensive vs inexpensive drugs, and there may be concerns that some patients will not be receiving optimal care.

### 3.4. Stakeholder involvement

Mapping and involvement of stakeholders is even more important within Phase IV studies than in Phase III field trials, as described in Chapter 9. They should be part of the planning of large-scale activities that will affect policy and strategy, and they should have an active role in the selection of study sites. They should have the possibility to comment on study design, participate in the review and interpretation of preliminary results, and advise on the development of appropriate feedback mechanisms. Their active involvement will be essential for a successful translation of results into policy and programmes.

### 3.5. Data collection, processing, and analysis

Phase IV effectiveness studies can make judicious use of health service attendance and other data that are routinely collected by health programmes or other sources. Possibilities for linking population data with health facility data should be explored, although systems for doing this are difficult to set up in most LMIC contexts. Prospective studies provide greater opportunities than retrospective studies to gather essential additional data. Efforts should be made to simplify data collection and management and to improve data quality by introducing real-time data collection directly on to computers or mobile devices. When using routine data sources, one issue to resolve early on, among all partners, is the question of data ownership, and it is essential to have a clear agreement of where data will be managed, stored, cleaned, and analysed, and agreed publication and dissemination policies (also see Chapter 20). Additional study data collection is usually needed to fill data gaps and address specific questions. Potential methods include health facility and household surveys, longitudinal health status studies, and qualitative research.

### 3.6. Contextual and confounding factors

In order to be able to adjust for confounding factors, contextual factors need to be closely monitored in observational Phase IV studies—factors that are external to the programme or intervention under consideration. These usually include socio-economic, environmental, demographic, and health system factors, as well as other locally relevant factors. Health outcomes are affected by socio-economic progress, changes in both public and private health services, and other initiatives in health or other sectors in the same geographical area. Because these changes can happen concurrently with the assessment of the effectiveness of the study intervention, they require special attention and need to be integrated in the interpretation and analysis of the data. The aim should be to collect contextual data to allow the evaluation of whether or not it is plausible that factors, other than the intervention being studied, could explain any improvements seen (Victora et al., 2004). Again, HDSS can play a central role here, as they can provide information on contextual factors and health system dynamics.

### 3.7. Reporting and dissemination

As for Phase III trials, a well-thought out system for reporting and dissemination of results is crucial if the results of Phase IV studies are to feed into policy and programmatic action. Whereas reporting standards for Phases I to III trials have been widely agreed (see Chapter 2), those for observational research are more recent. However, the STROBE statement (STrengthening the Reporting of OBservational studies in Epidemiology) is widely accepted and has been endorsed by a growing number of biomedical journals (<<http://www.strobe-statement.org>>). Efforts are also being made to develop and strengthen scientific methods for conducting comparative effectiveness research to improve the consistency, applicability, reliability, and validity of comparative effectiveness research findings for informing the health care decisions of patients, providers, and policy makers. An example is the DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network created in 2005 (<<http://effectivehealthcare.ahrq.gov/index.cfm/who-is-involved-in-the-effective-health-care-program1/about-the-decide-network>>).



### 3.8. Funding

Phase IV, and especially effectiveness, studies are often resource-intensive, due to large sample sizes and long follow-up periods. Also, a significant expansion of infrastructure and capacity is often required prior to the initiation of such studies, as many research groups are better placed to conduct efficacy trials than to conduct research within the health care delivery system. Raising funds for Phase IV research is challenging, but funders, including governments, have become increasingly interested in research to check that the interventions they fund provide the best possible value for money, so opportunities are improving.

## 4. Examples of real-world effectiveness studies

### 4.1. The INDEPTH Effectiveness and Safety Studies (INESS) platform

The development of new drugs and drug combinations for the treatment of malaria has created the need for countries to select and integrate new anti-malarial drugs into their health systems. INESS was designed as a platform for the conduct of Phase IV studies to provide objective data on the system effectiveness and safety of artemisinin combination therapies (ACTs) in real-world settings in Ghana, Burkina Faso, Tanzania, and Mozambique. The INESS research sites are based in districts with health and demographic surveillance systems and represent a diverse range of health system capacities and malaria endemicities. INESS looks at the overall performance (effectiveness) of deployment of the drug (ACT) in the system. It illuminates how the decay in the effectiveness of the ACTs occurs from efficacy to net or 'system' effectiveness, and at what levels the losses are the greatest (Figure 22.1). The research focuses on human behaviour, system behaviour, and drug behaviour in real-world contexts. Usually, there are lessons for all levels about how to optimize performance. By following a large number of patients with malaria who should benefit from the intervention through the system, this Phase IV study is in a powerful position to understand the net effectiveness of the intervention (see <http://www.indepth-network.org>).

Access and patient adherence seem to be the major bottlenecks creating the loss of effectiveness in the example shown in Figure 22.1. However, within each of the five compartments shown in the figure, the INESS study has identified and quantified the specific sub-determinants contributing to the loss in effectiveness. These include access failure (for example, due to distance, poverty, or lack of knowledge), diagnostics failure (for example, due to weaknesses in laboratory capacity or staff training), provider failure (for example, weaknesses in supply chain management, leading to drug or diagnostic test stock-outs, or poor prescribing), and patient adherence failure (for example, due to problems with taste, perceived side effects, stopping treatment when feeling better, or incorrect provider instructions).

INESS also conducts qualitative studies to understand community perceptions of the intervention under study, as well as the health system contexts, that help to explain the results from the quantitative system effectiveness studies. The INESS platform generates evidence that is sufficiently representative to inform local, national, and possibly global policy and practice. The results provide evidence on what human behaviour, health system, and drug issues need to be addressed and where the most urgent needs are. It also highlights issues for the industry to consider, in order to improve effectiveness. For the safety component, INESS strengthens the national spontaneous reporting system and also runs a separate event-monitoring cohort to detect and report AEs. Though initially developed to examine ACTs, the INESS platform has the potential to assess the effectiveness of other health interventions. Because the platform operates at the level of whole districts and follows a large number of exposures to the intervention, safety studies are easily incorporated.

### 4.2. Effectiveness of intermittent preventive treatment for malaria

The potential efficacy of intermittent preventive treatment for malaria in pregnancy (IPTp), infants (IPTi), and children (IPTc—now called seasonal malaria chemoprevention (SMC)) has been established in numerous safety and efficacy trials (Aponte et al., 2009). Yet, to move to public health action and promote it on a large scale, evidence is needed on the contextual determinants, costing, acceptability, and coverage rates. Taking IPTi using sulfadoxine–pyrimethamine (IPTi-SP) as an example, a cascade of activities has been undertaken by the IPTi consortium (<http://www.ipti-malaria.org>) to establish the real-world effectiveness of this intervention if it were to be used on a large scale. First, a pooled analysis of the efficacy and safety of IPTi-SP was undertaken (Aponte et al., 2009), based on six studies conducted in different African countries. The effect of IPTi-SP on immune responses to Expanded Programme on Immunization (EPI) vaccines and on the development of naturally acquired immunity to malaria was also studied, as well as the effect of sulfadoxine–pyrimethamine (SP) drug resistance on the efficacy of IPTi-SP. An

effectiveness study of IPTi was carried out in Tanzania and included cost-effectiveness (Manzi et al., 2008), acceptability (Gysels et al., 2009; Pool et al., 2008), and delivery through the existing health system, as IPTi is delivered through the EPI (Manzi et al., 2009). Then, a pilot study of the implementation of IPTi was carried out in six African countries, with careful evaluation of implementation bottlenecks and best practices, the evaluation of the impact of IPTi-SP on EPI coverage and other malaria interventions, its cost, acceptability, drug resistance, and pharmacovigilance safety profile. A separate study on the cost-effectiveness of IPTi followed and showed that IPTi-SP, when delivered alongside the EPI, is a highly cost-effective intervention. Overall, this series of Phase IV studies showed that IPTi-SP is a valuable addition to malaria control, but its benefits depend on the contextual factors of malaria endemicity and therapeutic efficacy of the drug. The decision on where to implement should take into account the local epidemiology of malaria. The IPTi consortium also conducted modelling of the impact of IPTi (Ross et al., 2008). One outcome of all these efforts is the IPTi decision support tool. It is a web-based tool, available at <http://ipti.lshtm.ac.uk>, and is intended to aid national and sub-national policy makers in assessing whether IPTi is a locally appropriate intervention. It includes drug resistance and cost-effectiveness components to assess the applicability of IPTi at a sub-national level.

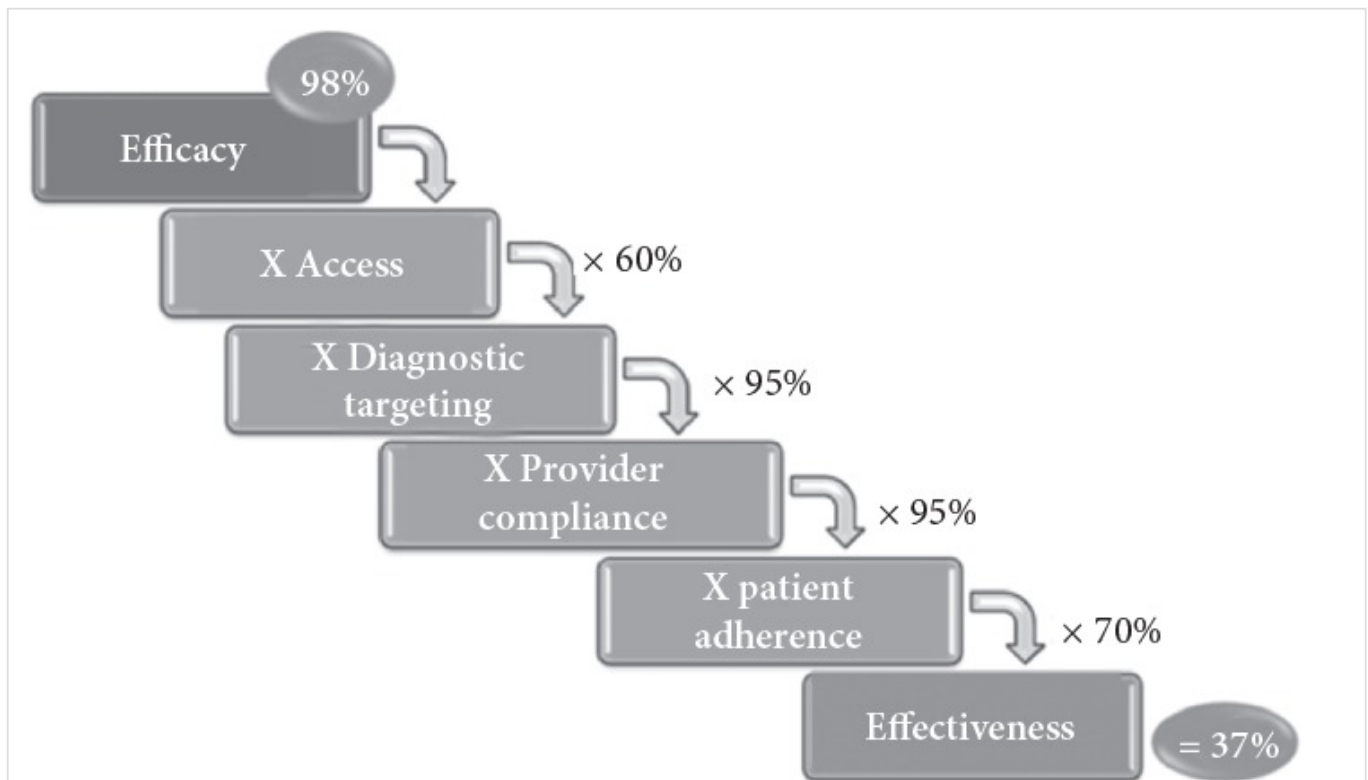
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## Figures



**Figure 22.1**

How the efficacy of highly efficacious malaria treatments translates into low community effectiveness for the treatment of malaria due to failings in the health system.

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