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Chapter 2 Types of intervention and their development

1. Introduction to types of intervention and their development

This book is about the evaluation of the effectiveness of health-related interventions. We use the term ‘intervention’ to apply to any activity undertaken with the objective of improving human health by preventing disease, by curing or reducing the severity or duration of an existing disease, or by restoring function lost through disease or injury. There are a wide variety of new interventions, and new strategies for the use of interventions, that are being developed against the major diseases common in LMICs. These include both public health and clinical care measures, and include drugs for acute and chronic conditions, vaccines, vector control, health education, behaviour change strategies, injury prevention, and better health planning and management methods that improve a spectrum of health-related activities. Research involving a wide range of disciplines is needed to develop, deploy, and assess these interventions, ranging from molecular biology and immunology to social sciences, epidemiology, and statistics. The focus of this book is on the evaluation of interventions through field trials. Field trials are required to assess how interventions, both old and new, may be best applied in populations and to determine their impact on improving the health of the population.

In this chapter, the characteristics of different kinds of intervention that may be used in disease control programmes are reviewed. How each type of intervention is implemented is outlined, and the implications of these implementation strategies for the design, conduct, and interpretation of field trials are discussed. The nature of an intervention will determine the way in which it can be evaluated in a field trial. Some interventions which are applied to individuals can be evaluated through the random allocation of individuals to the intervention or the ‘control’ arms. Other interventions are applied to groups of individuals, such as households or whole communities, and the group should therefore be the unit of randomization.

2. Types of intervention

Interventions can be classified into two broad categories: (1) preventive interventions are those that prevent disease from occurring and thus reduce the incidence (new cases) of disease, and (2) therapeutic interventions are those that treat, mitigate, or postpone the effects of disease, once it is under way, and thus reduce the case fatality rate or reduce the disability or morbidity associated with a disease. Some interventions may have both effects.

2.1. Preventive interventions

2.1.1. Vaccines

Vaccines are administered to individuals, usually before they have encountered the infectious agent against which the vaccine is targeted, in order to protect them when they are naturally exposed to the agent. Many are among the most cost-effective interventions, because, after a single dose or a series of doses of the vaccine, an individual may acquire long-term protection against the agent. They work by inducing a variety of immune mechanisms, through the humoral and/or cellular immune systems. The immunological responses and associated immunological memory induced by vaccination confer protection from later infections, though a booster vaccination may be necessary if the interval between the original vaccination and exposure to the agent is long. Most vaccines have to be administered before the infectious agent is encountered naturally, and thus field trials of such vaccines will involve the enrolment of healthy individuals and often involve infants or very young children—though the vaccine may be given at a later age if the age of natural infection is at later ages, for example, for most sexually transmitted infections (STIs), or if a new infectious agent, to which no one has been previously exposed, enters a community such as a new strain of influenza.

Not all vaccines are targeted at persons without previous exposure to the infectious agent. For example, there is substantial research to develop vaccines against parasitic diseases. The mode of action of some of these vaccines is to prevent parasitic proliferation within the host after invasion (and hence curtailment of disease), and some vaccines against vector-borne diseases are even targeted to prevent replication of the forms of the infection in the vector, so that onward transmission to humans is prevented.

For infectious diseases that affect both high-income countries (HICs) and LMICs, the first trials of new vaccines are usually conducted in HICs. This is because currently most new vaccines are developed and produced in HICs (though this situation is changing), and it is generally accepted that at least early clinical studies should be conducted in the country of vaccine manufacture. However, the results of trials in HICs may not be directly applicable to LMICs for a variety of reasons such as differing prevalences of other infections or of nutritional deficiencies, which might interfere with the mode of action of the vaccine. Thus, there will often be a need for further trials of the vaccine in LMICs, even if efficacy has been established in HICs. In addition, there has been increased focus in recent years on the development of vaccines against infectious agents that only, or almost only, occur in LMICs, such as malaria or visceral leishmaniasis, or where the overwhelming disease burden is in such countries, such as tuberculosis (TB) or HIV infection. For vaccines against these agents, the first major field trials to assess efficacy are likely to be conducted in LMICs.

2.1.2. Nutritional interventions

Food and nutrition are major determinants of human health and disease. Particularly in low-income countries and deprived populations in middle-income countries, under-nutrition remains a major cause of disease. Severe malnutrition, such as kwashiorkor or marasmus, is life-threatening, but milder forms of malnutrition are major risk factors that adversely influence the susceptibility to, and the outcome of, many infectious and other diseases, as well as cognitive development. In addition to calorie and protein deficiencies, specific deficiencies in micronutrients, such as iron, folate, zinc, iodine, and vitamin A, may be important determinants of severe diseases. Trials to address these problems may involve the regular provision of high-protein/calorie diets or supplementation to individuals with specific micronutrients, involving repeated visits to the same persons over several years, the frequency of administration depending on the nature of the supplement(s). Other trials, often with the intervention being applied at a community level, may involve food fortification (for example, iron, iodine, vitamin D) and experiments to change agricultural practices or eating or food preparation habits to increase the intake of particular micronutrients.

2.1.3. Maternal and neonatal interventions

A mother's health and well-being during pregnancy and around the time of delivery, including access to appropriate care, are critical determinants of maternal mortality and neonatal and child health in the early years of life, and possibly for much longer. Preventive interventions before or during pregnancy include family planning, treatment of infections, such as syphilis and malaria, good nutrition, including micronutrients, good antenatal monitoring and care, and access to skilled care at the time of delivery and post-partum. Trials of maternal interventions may involve both community-based studies, with the early identification of pregnancies and the instigation of preventive interventions to avoid pregnancy complications, or may be hospital- or health centre-based, directed at improving the performance of the health system in caring for women during and after pregnancy and at the time of birth.

Interventions directed to the neonate are also important, such as exclusive breastfeeding and care practices, such as 'kangaroo mother care', a method of care of preterm infants, involving infants being carried, usually by the mother, with skin-to-skin contact.

2.1.4. Education and behaviour change

Some interventions directed at preventing disease are based solely upon changing human behaviour (for example, anti-smoking campaigns or campaigns to promote breastfeeding). Nearly all health interventions must have an associated educational component for their effective deployment, but the extent of educational effort required ranges from the provision of simple information (for example, when and where a clinic for immunization will be held) to efforts at increasing understanding (for example, of the importance of male circumcision for the prevention of HIV) and to attempts to change lifestyles (for example, diet or sexual habits). Education to increase knowledge and impart new skills may be necessary but is rarely sufficient to induce behaviour change. Individuals must also have the capacity, willingness, and motivation to act on the knowledge and to use the skills. The design and implementation of an educational intervention, and other 'complex' interventions (Craig et al., 2008), will usually need to be researched through careful investigations in the community, using the kinds of methods discussed in Chapters 9 and 15.

Examples of educational components of disease control programmes include:

- ◆ educating children or mothers about the causes of the disease, such as diarrhoea, and how to prevent it
- ◆ promoting adherence to long-term treatment such as for HIV infection or TB

- ◆ developing effective participation in programmes that:
 - need broad coverage to maximize the effects of immunization or drug distribution
 - require people to recognize disease symptoms for early treatment
 - necessitate active co-operation in home improvements or insecticide programmes
 - involve direct action and responsibility in deploying vector, or intermediate host, traps
 - need community efforts for environmental improvements such as developing and maintaining improved water supplies or better disposal methods for faeces.

Organizing trials of behaviour change interventions are among the most challenging, and there are few examples illustrating the design of replicable interventions that achieve lasting behavioural change in the context of a trial. For example, changing tobacco smoking behaviour at a population level required decades of concerted, multifaceted campaigns. However, attempts to reduce diarrhoeal diseases and respiratory infections through the promotion of hand-washing with soap have produced encouraging results.

2.1.5. Environmental alterations

Alterations to the environment directed at reducing the transmission of infections are central to the control of many infectious diseases, particularly those that are transmitted through water, such as cholera, or through the faecal–oral route such as many gastrointestinal infections. Environmental interventions to reduce human faecal and urine contamination include latrine construction, provision of sewage systems, clean water supplies, and protected food storage. Other environmental interventions tackle indoor or outdoor air pollution or involve the disposal of contaminants such as pesticides or heavy metals. Many of these interventions require substantial educational efforts and lifestyle changes. They are also interventions that typically have to be applied to whole communities, rather than to individuals in a community, so that, in trials, the unit of randomization is the community or, in some instances, the household.

2.1.6. Vector and intermediate host control

Some major communicable diseases in developing countries depend on vector and intermediate hosts for their transmission. For different infections, the vectors include mosquitoes, tsetse flies, triatomine bugs, sandflies, ticks, and snails. There are a wide variety of control measures to reduce transmission of these infections through attacking the vectors or the reservoirs of infection. Most interventions require a good understanding of the vector or intermediate host, its life cycle, and the environmental conditions that it requires to propagate infections. Control measures may include the application of insecticides or larvicides, new or improved selective biological agents against disease vectors, engineering techniques for reducing vector habitats, community involvement in eliminating vector breeding sites and in deploying traps, housing and screening improvement for reducing human–vector contact, and strategies involving combinations of methods with, for example, the objective of reducing or delaying insecticide resistance. For many of these methods, intermediate process indicators, such as reduction in vector density, can be used for the assessment of impact, but it is often also necessary to determine the impact of the measures on the health status of the population. For example, for malaria, many different approaches to vector control have been used, based upon attacking the mosquito in various stages of its life cycle. These include control of breeding sites to reduce vector density by drainage and waterway engineering and application of specific larvicides and biological agents; the use of mosquito netting, screens, and repellents for personal protection from bites; aerosol distribution of insecticides to reduce adult mosquito densities; and different approaches to killing adult mosquitoes, through either spraying residual insecticides, such as with dichlorodiphenyltrichloroethane (DDT), on the internal walls of houses where mosquitoes rest after a blood meal or through the use of insecticide-treated bed-nets (ITNs) that kill and/or repel mosquitoes seeking a blood meal. These different approaches require quite different study designs. Residual insecticide on the walls of houses offers relatively little direct protection to those in the treated household, as the mosquitoes take up the insecticide while resting *after* a blood meal. The protection is to those in other households whom these mosquitoes would have bitten for their next blood meal. To reduce transmission in high transmission areas, virtually all households in the neighbourhood must be sprayed. The higher the intensity of transmission, the more difficult it is to achieve sufficient coverage. The use of ITNs, developed as an intervention against malaria over the last two decades, leads to reductions in transmission, clinical disease, and overall childhood mortality. Trials of these kinds of

intervention often involve communities, rather than individuals, as the unit of randomization. These trials are especially challenging to design, because some vectors, such as mosquitoes, may have a flight range that may lead to the ‘contamination’ of intervention communities, with vectors coming in from outside of the community.

2.1.7. Drugs for the prevention of disease

Drugs or other interventions may be used for the prevention of infection (prophylaxis) or disease consequent on infection. An example of the former would be isoniazid prophylaxis to HIV-infected individuals to reduce their risk of TB, and of the latter, the treatment of HIV-infected individuals with antiretroviral drugs to slow the progression of their disease. Sometimes, the use of drugs for prophylaxis or to reduce disease progression does not involve individual diagnosis, but community or group diagnosis is needed to identify groups that should receive the treatment. For example, mass administration of anti-helminthic treatment to schoolchildren is sometimes administered in this way. Whether requiring specific diagnosis or not, therapeutic or preventive agents are usually taken on an individual basis, though sometimes agents can be distributed to everyone in a community through the water supply (for example, fluoride against dental caries) or in food (for example, historically, diethylcarbamazine for filariasis and chloroquine for malaria in medicated salt). Mass treatment of school-age children in areas highly endemic for the infection with an anti-schistosomal drug every year or two may be sufficient to virtually eliminate serious disease consequences of infection with *Schistosoma mansoni*.

Prophylaxis may be aimed at preventing or limiting infection, particularly in those at high risk for a limited period of time (for example, anti-malarials taken by those who are temporarily visiting malaria-endemic areas). The value of such an approach is limited by the duration of action of the agent (which determines the frequency with which it must be taken), by adverse reactions, and sometimes by the role of the intervention in stimulating the development of drug-resistant organisms. For some purposes, prophylaxis may be used by permanent residents of endemic areas (for example, anti-malarials in pregnancy).

Drugs also may be used prophylactically for treatment of preclinical infection (for example, during the incubation period before the onset of symptoms, as for the *gambiense* type of trypanosomiasis) or for treatment of subclinical infection (for example, ivermectin against onchocerciasis, and praziquantel against schistosomiasis).

Strategies for the use of such interventions include the mass treatment of entire populations or the targeted treatment of identifiable subgroups (such as school-age children) in areas where the infection is highly prevalent. Generally, such treatment is applied for the benefit of the individuals treated, but the objective may also be to reduce the transmission of the agent in the community more generally. When the prevalence is very high and the treatment is cheap, treating all those in a defined population may be more cost-effective than screening the whole population and then treating only those found infected.

2.1.8. Injury prevention

Injuries are major causes of death and disability, especially in LMICs. They disproportionately affect the young and have a large economic impact on society. For children and young people, road traffic accidents, drowning, fires, poisoning, interpersonal violence, and war are leading global causes of serious injuries, but often these are not considered ‘health problems’ and are not sufficiently integrated into public health thinking. Yet there are many potential interventions that might lead to reductions in deaths and disabilities from injuries, such as traffic calming or infrastructural changes to separate pedestrians from fast-moving vehicles to reduce motor vehicle injuries, and improving the security of water sources to reduce drowning accidents; there is great need for more trials of interventions directed at reducing injuries.

2.2. Therapeutic interventions

2.2.1. Treatment of infectious diseases

The mechanism of action of a drug used for disease control will influence the design of field trials to evaluate its impact. Most drugs employed against infectious disease are used to kill or inhibit the replication or spread of the pathogen in the host. Strategies for disease control that use such agents may involve case detection (which requires an appropriate case definition and a diagnostic method), followed by treatment that is designed to reduce morbidity and mortality. Often, the public health success of this approach depends critically upon case finding, and, for diseases such as TB and leprosy, it depends also on case holding, i.e. being able to follow and treat each patient at regular intervals

over sufficient time to eliminate the agent from the individual. Case finding and treatment may also reduce transmission of an agent if cases are the main reservoirs of infection, if case detection methods locate a high proportion of prevalent cases, and if the treatment is sufficiently effective.

2.2.2. Surgical and radiation treatment

RCTs of surgical and radiation treatments are usually done as clinical trials; field trials of these interventions are relatively uncommon. However, procedures, such as cataract extraction or simple inguinal hernia repair, are examples of where field trials have been usefully undertaken. In general, the only distinctive feature that may set these apart, in terms of study design, from other field trials is the issue of 'blinding' (see Chapter 11, Section 4). For some forms of surgery, 'sham' operations have been used in clinical studies and perhaps could be considered in field trials. In general, however, randomized trials of these procedures will have to be conducted without blinding.

2.2.3. Diagnostics to guide therapy

The efficient treatment of most diseases requires first that they be accurately diagnosed. Often the diagnosis is made on the basis of clinical symptoms and signs, but the imprecision of this method for many conditions is increasingly recognized. There is an urgent need for new, or improved, sensitive and specific diagnostic tests for many infectious and chronic diseases, that are both simple to use and cheap. For example, intervention strategies that depend upon case finding and treatment usually require suitable diagnostic tests. Specific studies may be necessary to measure the specificity, sensitivity, and predictive values of different diagnostic tests, as these properties will impact on the likely effectiveness of a case finding and treatment intervention. For example, the development and widespread introduction of rapid diagnostic tests for malaria, to replace microscopy or the presumptive treatment of fever, has been an important innovation in malaria control and has also focused attention on the need for improved diagnostic methods and appropriate treatment of non-malarial fevers.

Field trials to evaluate the performance characteristics of diagnostics are not discussed specifically in this book, other than in the context that they may be incorporated as part of an intervention strategy to improve the control of a specific disease. The design of studies to evaluate the properties of diagnostics has been discussed elsewhere (Peeling et al., 2010).

2.2.4. Control of chronic diseases

Chronic conditions may have an infectious aetiology (for example, HIV, TB) or may have environmental or other causes (for example, cardiovascular diseases and many cancers). Many chronic diseases, once diagnosed, may not be curable, but they can be controlled by a combination of education/behaviour change interventions, plus regular, often daily, use of pharmaceuticals. The nature of the clinical care required is often more complicated than required for acute conditions, such as diarrhoea and pneumonia, which, once diagnosed, usually require a single course of treatment. Interventions for chronic disease often must include screening of communities to identify cases; assessment of each case for the stage of the disease and possible attendant complications that are likely to require a variety of laboratory tests; and developing a long-term treatment and assessment plan. The treatment of such conditions often requires long-term monitoring, with a dependence on reliable laboratory results and a system to track the clinical and laboratory findings within a single individual over time. Trials of such interventions must often be conducted over several years, or even decades, to completely assess treatment efficacy.

2.3. Other forms of intervention

2.3.1. Legislation, legal action, taxation, and subsidies

Enforcement of anti-pollution laws, food labelling, and legal restrictions have an important role to play in public health. Behaviour may be strongly influenced by legal restrictions, and increasing prices through taxation have been shown to be effective in reducing tobacco and alcohol consumption, for example. However, it is difficult to design randomized trials of such interventions, because the interventions usually have to be implemented at the national level, making it very difficult to identify a suitable control group.

There has been increasing interest recently in providing various types of subsidies to individuals to change their health-related behaviour (often known as conditional cash transfers). Examples include incentives for children to remain in school, or to health care providers to provide services of at least a certain minimum quality (performance

incentives). Some of these interventions have been evaluated through RCTs, and there is further scope for using such approaches.

2.3.2. Health systems interventions

Increasing recognition of the importance of interventions that operate at health systems level, such as policy implementation, financing, educational reform, and strengthening of leadership, management, and governance, has led to a variety of health sector training programmes, organization changes, decentralization and devolution, and various incentives and personnel policies. Most of these efforts have been introduced on a system-wide basis, with little thought about the value of rigorous assessment. But, with adequate planning, rigorous evaluation of these kinds of interventions should be possible through randomized trials, especially by making use of the 'stepped wedge' approach of a phased introduction of measures in different communities over a period of time (Brown and Lilford, 2006). Many health systems research studies may be considered as implementation research, and most could be considered as complex interventions, as discussed in Sections 2.3.3 and 2.3.4.

2.3.3. Implementation research

Within the context of field trials, implementation research does not aim to develop new interventions but focuses on optimizing the delivery of existing interventions that have previously been shown to be efficacious when implemented well. Implementation research explores the challenges of how best to implement research findings in the real world and how to contextualize interventions for specific settings. Hence, an example of an implementation research trial was one where a comparison was made of the costs and effectiveness of health workers delivering antiretroviral therapy to patients who attend a central clinic or hospital, compared with lay workers delivering the antiretrovirals to patients in their homes and only referring them to the clinic if they reported problems on a screening questionnaire (Jaffar et al., 2009).

A general reference on implementation research is Werner (2004).

2.3.4. Complex interventions

The design of a trial to evaluate the efficacy of a new vaccine or drug is relatively straightforward, in the sense that there are many past examples of such evaluations to draw upon when planning a new study. However, the evaluation of some interventions, such as the deployment of a new procedure in the health service or in public health practice, may involve consideration of several interacting components, including, for example, educational components and behavioural change. Such interventions pose special problems for evaluation, and these kinds of intervention have been called 'complex'. Many of the extra problems relate to the difficulty of standardizing the design and delivery of the interventions, their sensitivity to features of the local context, the organizational and logistical difficulty of applying experimental methods to service or policy change, and the length and complexity of the causal chains linking intervention with outcome.

In 2000, the UK Medical Research Council published a *Framework for development and evaluation of RCTs for complex interventions to improve health* to help researchers and research funders to recognize and adopt appropriate methods. These guidelines were updated and revised subsequently and can be downloaded from the Internet (<<http://www.mrc.ac.uk/documents/pdf/complex-interventions-guidance>>).

Box 2.1 is reproduced from the guidelines and summarizes the steps in developing and evaluating trials involving complex interventions.

3. Evolution of new intervention products and sequence of study phases

Many intervention products, and especially drugs and vaccines, are likely to originate from basic research in laboratories. Such products must go through a long series of tests, before they can be considered for use in the kinds of field trials that are the focus of this book. Before any human use, a new product will be tested in the laboratory for its activity and toxicity in various *in vitro* and animal test systems. If it successfully passes through these stages, studies of safety, toxicity, and activity may be conducted in a small number of human volunteers, with careful clinical monitoring. A series of further studies, each including increasing numbers of subjects, must be carried out before a new product can be introduced for widespread use. Trials in humans usually go through a series of sequential 'phases' of progressively increasing size to establish first the safety and mode of action and then, in later phases, the efficacy against the target disease(s) and safety in a larger number of subjects.

3.1. Clinical studies: Phases I to IV

Phase I studies are exploratory first-in-human trials and may involve the administration of small, then larger, doses of the study product to a small number of healthy human subjects (ten to 50) to gather preliminary data on the product's pharmacokinetics (where the product and its metabolites go within the body and in what concentrations) and pharmacodynamics (what the drug does in the body). These studies can help to establish the dosage and frequency that are safe and necessary to have an effect. These trials are designed to make an initial assessment of the safety and tolerability of the drug or vaccine in a small number of, usually healthy, volunteers.

Phase II trials are conducted for products that have shown no significant safety problems in Phase I trials. They involve progressively larger numbers of participants (for example, initially tens of subjects, but later studies may involve 100s) and are designed to assess how well the intervention works (therapeutic drugs would involve studies in patients, whereas vaccines would be assessed for immunogenicity in healthy volunteers), as well as to check for safety in a larger number of healthy volunteers (vaccines) or in patients (therapeutic drugs). Phase II trials may also be designed to evaluate what doses and the number of doses of the intervention should be given, and what the intervals should be between doses. Usually, a product will be evaluated in a number of different Phase II trials, evaluating its performance under different circumstances, for example, a malaria vaccine might be initially trialled in adults but then tested in progressively younger groups until tested in the final target population of infants.

Phase III trials aim to provide a definitive assessment of the efficacy of the intervention against the primary outcome(s) of interest. They also provide safety data in a larger group of subjects. These trials usually involve large numbers of individuals (e.g. 1000–3000 or more) and are studies that are conducted to produce the evidence of efficacy and safety required to submit a product to a licensing authority. For this reason, they are sometimes called 'pivotal' trials.

Phase IV studies are conducted after the intervention has been shown to be efficacious in Phase III trials and are conducted to assess the safety and effectiveness of an intervention when used under routine health service conditions, or close to these conditions (rather than in the special circumstances of a controlled trial). Where they involve a regulated product, such as a drug or vaccine, they are usually post-registration or post-licensure studies. Safety issues that are important, but which arise in a relatively small proportion of individuals, may only become apparent through Phase IV studies, once there is widespread use of an intervention. Phase IV studies sometimes take the form of randomized trials where the safety and effectiveness are assessed by comparing the results of administering the product to some individuals or communities, but not to others (allocated at random). However, such trials may be difficult to conduct, once a product has been licensed by the national regulatory authority, and then non-randomized assessments must be made, such as through 'before versus after studies' or case-control investigations. Many trials of strategies of how best to use drugs or vaccines can also be considered as Phase IV studies, such as a comparison of intermittent preventive therapy (IPT) using anti-malarial drugs given to all young children, compared to teaching their mothers to recognize and treat their children if they have possible falciparum malaria.

The main focus of the book will be on large-scale Phase III trials conducted 'in the field' (i.e. outside clinical facilities), but there is also a specific chapter on Phase IV studies (see Chapter 22).

Although similar terms are often used for the 'phase' of trials conducted to test the effectiveness or efficacy of interventions that do not use an investigational product, such as behaviour change interventions or incentives, these have much less well-defined, or universally agreed, phases, and it is not uncommon for the first RCT of such an intervention to be the equivalent of a Phase III trial of a drug or vaccine.

3.2. Registration of new interventions

Legal registration procedures are mandated in most countries before a drug or vaccine can be put into general use, and these procedures normally require documentation of the safety and efficacy of the intervention, based on RCTs involving many hundreds of subjects. Further guidance on the rules and regulations for assessing the safety and efficacy of products for use in human beings can be found at the website of the US Food and Drug Administration (<<http://www.fda.gov>>).

3.3. 'Proof of principle' trials

The purposes of field trials may change as experience with an intervention accumulates. Sometimes, particularly in early trials of a new intervention, the purpose of the study is analytic to demonstrate an effect or to establish a

principle, with little consideration as to whether the intervention is practicable at the population level for disease control. An example might be the use of a malaria vaccine that must be administered monthly to be effective. Such studies are sometimes called ‘explanatory’ or ‘proof of principle’ trials (Schwartz and Lellouch, 1967). Once an effect against the disease under study has been demonstrated, there might then be greater impetus to develop new formulations of the intervention or different schedules that would be more practicable for application in a disease control programme. Subsequent, and generally larger, trials are conducted, in which the purpose is to establish the benefit of an intervention applied under the circumstances of general use. These studies are often called ‘pragmatic’ trials (Schwartz and Lellouch, 1967).

3.4. Trials of intervention delivery strategies

Although new products developed through basic science research may serve as the impetus for field trials, some interventions or intervention strategies are developed directly as a result of field studies and experience such as a vaccine strategy for smallpox eradication and the use of tsetse fly traps for the control of trypanosomiasis transmission. Thus, trials may be needed not only of the product itself, but also of the way that product is used or delivered. Trials like these would involve intervention ‘packages’ which might include, for example, the same drug or vaccine, but provided with different educational approaches or delivery methods. Sometimes, an intervention that has been shown to be effective must be added into an ongoing disease control programme that involves other kinds of interventions. For example, it is expected that, when effective malaria vaccines become available, they will be added to other malaria control methods, based on a combination of vector control, case finding, and treatment strategies. Further studies of how best to integrate these interventions into an overall strategy will have to be worked out. In addition, policy and planning decisions about disease control will have to be guided by appropriate cost-effectiveness analyses.

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Boxes

Box 2.1 The development–evaluation–implementation process

Developing, piloting, evaluating, reporting, and implementing a complex intervention can be a lengthy process. All of the stages are important, and too strong a focus on the main evaluation, to the neglect of adequate development and piloting work, or proper consideration of the practical issues of implementation, will result in weaker interventions that are harder to evaluate, less likely to be implemented, and less likely to be worth implementing.

Developing an intervention

Questions to ask yourself include: Are you clear about what you are trying to do—what outcome you are aiming for, and how you will bring about change? Does your intervention have a coherent theoretical basis? Have you used this theory systematically to develop the intervention? Can you describe the intervention fully, so that it can be implemented properly for the purposes of your evaluation and replicated by others? Does the existing evidence—ideally collated in a systematic review—suggest that it is likely to be effective or cost-effective? Can it be implemented in a research setting, and is it likely to be widely implementable if the results are favourable?

If you are unclear about the answers to these questions, further development work is needed, before you begin your evaluation. If you are evaluating a policy or a service change as it is being implemented, rather than carrying out an experimental intervention study, you still need to be clear about the rationale for the change and the likely size and type of effects, in order to design the evaluation appropriately.

Piloting and feasibility

Questions to ask yourself include: Have you done enough piloting and feasibility work to be confident that the intervention can be delivered as intended? Can you make safe assumptions about effect sizes and variability, and rates of recruitment and retention in the main evaluation study?

Evaluating the intervention

Questions to ask yourself include: What design are you going to use, and why? Is an experimental design preferable, and, if so, is it feasible? If a conventional parallel group RCT is not possible, have you considered alternatives such as cluster randomization or a stepped wedge design? If the effects of the intervention are expected to be large or too rapid to be confused with secular trends, and selection biases are likely to be weak or absent, then an observational design may be appropriate. Have you set up procedures for monitoring the delivery of the intervention and overseeing the conduct of the evaluation?

Including a process evaluation is a good investment to explain discrepancies between expected and observed outcomes, to understand how the context influences outcomes, and to provide insights to aid implementation. Including an economic evaluation will likewise make the results of the evaluation much more useful for decision makers.

Reporting

Questions to ask yourself include: Have you reported your evaluation appropriately, and have you updated your systematic review? It is important to provide a detailed account of the intervention, as well as a standard report of the evaluation methods and findings, to enable replication studies or wider-scale implementation. The results should ideally be presented in the context of an updated systematic review of similar interventions.

Implementation

Questions to ask yourself include: Are your results accessible to decision makers, and have you presented them in a persuasive way? Are your recommendations detailed and explicit?

Strategies to encourage implementation of evaluation findings should be based on a scientific understanding of the behaviours that need to change, the relevant decision-making processes, and the barriers and facilitators of

change. If the intervention is translated into routine practice, monitoring should be undertaken to detect adverse events or long-term outcomes that could not be observed directly in the original evaluation, or to assess whether the effects observed in the study are replicated in routine practice.

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