The SAFE strategy for trachoma control: using operational research for policy, planning and implementation

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Abstract Trachoma is a neglected disease and also the world's leading infectious cause of blindness. It causes misery, dependency and is a barrier to development. Trachoma is controlled by a WHO-endorsed integrated strategy of surgery for trichiasis, antibiotic therapy, facial cleanliness and environmental improvement, which is known by the acronym SAFE. The strategy is based on evidence from field trials and is continually being refined by operational research that informs national policy and planning; the strategy has affected both programme delivery and implementation. As a result of the findings of operational research, surgery is now frequently conducted by paramedics in communities rather than by ophthalmologists in hospitals; yearly mass distribution of a single oral dose of azithromycin has replaced the use of topical tetracycline; and the promotion of better hygiene, face-washing and the use of latrines are used to reduce transmission. Those who implement programmes have been equal partners in conducting operational research thus reducing the "know–do" gap and minimizing the lag that often exists between the completion of trials and putting their results into practice. Operational research has become a part of practice. Although there are still many questions without answers, national programme coordinators have a reasonable expectation that trachoma control programmes based on SAFE will work.

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يمكن الاطلاع على الملخص بالعربية في صفحة 618.

Introduction

Trachoma, caused by ocular infection with *Chlamydia trachomatis*, is the world's leading infectious cause of blindness.[1] Repeated infection causes inflammation and scarring of the conjunctival lining of the upper eyelid, which distorts the lid margin and causes the lashes to touch the surface of the eye (trichiasis). In addition to disabling discomfort, constant abrasion of the cornea causes physical damage that leads eventually to corneal opacification and blindness.

Trachoma affects the most marginalized and disadvantaged populations in 55 endemic countries.[2] More than a million people have become blind from trachoma, and about 10 million are in imminent danger of going blind from trichiasis. Vaccine trials conducted in the 1960s were unsuccessful, and during the subsequent three decades trachoma was almost forgotten. This neglect was largely due to the lack of interventions of proven efficacy. In the early 1990s it was demonstrated that a single oral dose of azithromycin was as effective as the previously recommended (but seldom used) regimen of 6 weeks of daily topical application of tetracycline ointment to treat ocular infection with *C. trachomatis*.[3] In light of these results, the sponsor of the trial, Joseph Cook of the Edna McConnell Clark Foundation, and leading trachoma researchers encouraged Pfizer, the manufacturer of azithromycin, to support further studies to examine the efficacy and effectiveness of providing mass treatment to control trachoma; they also encouraged Pfizer to donate the drug to trachoma control programmes. In 1998 the foundation and Pfizer established the International Trachoma Initiative. Countries eligible for donations of the drug are those that satisfy the initiative's expert committee and board that:

- they have a prevalence of active trachoma exceeding the WHO threshold for intervention (considered to be a prevalence of >10% trachomatous inflammation, follicular, [known as grade TF] among children aged 1–9 years);
- they are willing to operationalize the full SAFE strategy; and
- they have a realistic plan for handling and distributing azithromycin.

Ten million doses were donated initially; 135 million more were pledged in 2003; and in 2006 Pfizer has committed itself to provide an uncapped quantity of azithromycin as long as significant progress continues to be made. Pfizer donates and ships azithromycin to 12 countries, and these countries have demonstrated an exponential increase in the number of doses distributed since 1999 (Fig. 1).

In 1998 the World Health Assembly passed a resolution calling for the global elimination of blinding trachoma by 2020. WHO and the International Agency for the Prevention of Blindness, a consortium of nongovernmental development organizations, launched the Global Alliance for the Elimination of Blinding Trachoma by 2020 (GET 2020). The aim of the alliance is to eliminate blindness caused by trachoma — not to eradicate trachoma or trachoma infection. To date, 32 countries have joined the alliance and share a commitment to trachoma control.[4] Annual meetings of the alliance have been held since 1998 and are preceded by a 1-day informal scientific workshop during which recent findings are presented. A summary of these findings is subsequently presented at the full meeting. On a smaller scale, 7–12 countries in which trachoma is endemic have been meeting annually

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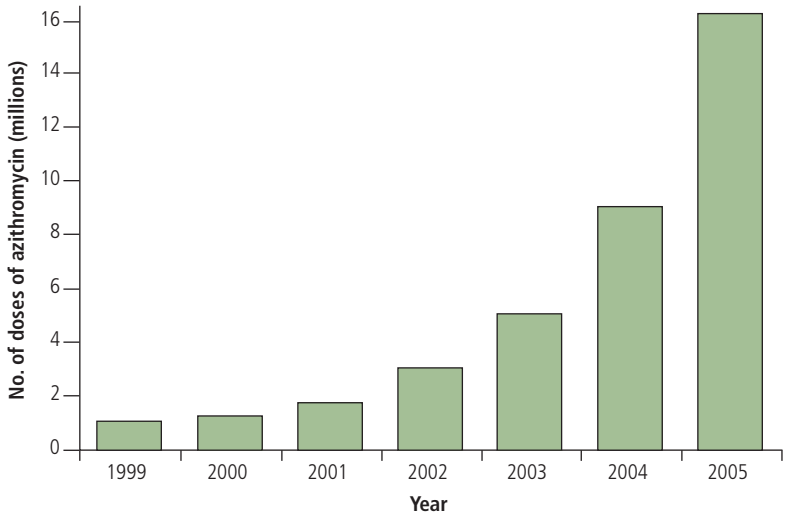
at the Carter Center (in Atlanta, GA) since 2000 to discuss progress and research developments. At these meetings a more accessible format allows country representatives to provide updated information on their achievements and inspiration to other programme managers (Fig. 2 and Fig. 3). In this way new techniques and practices are shared and translated into policy and practice without delay. Advocacy by WHO and the nongovernmental development organizations through these meetings has raised the level of awareness of trachoma in endemic countries and enabled local resources to be mobilized.

The strategy for trachoma control promoted by all these organizations is the integrated strategy known as SAFE; this strategy aims both to treat and prevent the disease. SAFE stands for surgery for trichiasis, antibiotic therapy, facial cleanliness and environmental change. It was based on the results of the best research from the field, and it is modified in the light of ongoing operational research, which is frequently conducted in partnership with implementing agencies. Operational research has been used to bridge the "know–do" gap and translate knowledge into action. This paper describes the process by which the evidence base for trachoma control using the SAFE strategy has been developed and why there is a good expectation that it will be effective (Box 1).

Fig. 1. **Number of doses of azithromycin distributed for trachoma control since donation programme began in 1999. (Data for 2005 are provisional)**



Source: International Trachoma Initiative country reports.

WHO 06.93

Surgery for trachomatous trichiasis

Approximately 10 million people have trachomatous trichiasis. Trachoma control programmes need to prioritize treatment of these individuals because if the disease is left untreated they are at high risk of developing irreversible blinding corneal opacification.[5,6] Lid surgery for trachomatous trichiasis is believed to reduce the risk of progressive corneal opacification and blindness.[7,8] There is a growing body of operational research that has guided trachoma control programmes as they implement the initial surgical component of the SAFE strategy.

Indications for surgery vary between control programmes. Some advocate early surgery — when one or more lashes touch the eye — while others practice epilation until more severe trachomatous trichiasis develops. Data from the Gambia on the natural history of trachomatous trichiasis suggest that disease progression can be quite swift.[5] Therefore, where contact with eye-care services is infrequent, surgery for mild disease is probably appropriate. In addition, surgery for mild disease is technically easier and is likely to have a better outcome.[8] Several different surgical procedures are in use. A randomized controlled trial (RCT) in Oman compared several alternatives and identified bilamellar tarsal rotation as having the lowest rate of recurrence of trachomatous trichiasis.[7] WHO endorses this operation for trachoma control programmes. This surgery and posterior lamellar tarsal rotation were formally compared in an RCT in Ethiopia.[9] The study found no difference in the recurrence rate of trichiasis three months after surgery; however, long-term follow-up data are still needed.

Most countries where trachoma is endemic have an insufficient number of ophthalmologists to deliver the volume of surgery required. Therefore, many programmes train nurses and other paramedical staff to perform eyelid surgery. An RCT from Ethiopia found no difference in the outcome of trachomatous trichiasis surgery performed by trained nurses when compared with surgery performed by ophthalmologists.[10] A retrospective review of trachomatous trichiasis surgery in Morocco found that patients operated on by nurses had significantly fewer recurrences of trichiasis than patients operated on by ophthalmologists, possibly because ophthalmologists tended to operate on more difficult cases.[11] These studies support the pragmatic decision to train non-ophthalmologists in trachomatous trichiasis surgery.

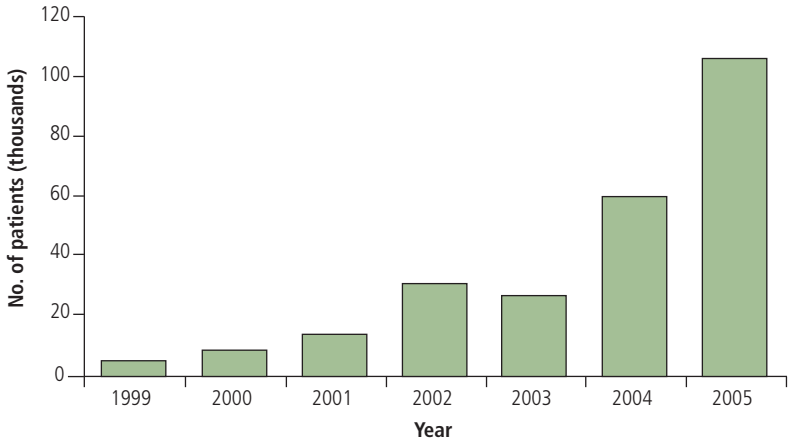
In many endemic settings acceptance of surgery is low. Barriers to the uptake of surgery include a lack of knowledge, the cost, fear, inaccessibility and being too busy.[12] Inaccessibility is a consistent barrier, and village-based surgery might be expected to improve uptake. In a community RCT in the Gambia the acceptance rate for surgery was 45% higher when the surgery was village-based than when it was health centre-based (although the difference did not reach statistical significance).[13] There was no difference in rates of recurrent trichiasis or complications between those who had surgery in the village and those who had it at the health centre. The cost to the patient was significantly lower for those who had village-based surgery.

Trichiasis recurrence is reported to vary between about 20% at one year and 62% by three years.[7,8,14–16] Several factors may contribute to recurrence. The choice of procedure is important. Inter-surgeon variability also occurs, emphasizing the importance of implementing ongoing audit to identify surgeons in need of additional training and support.[8,14] Conjunctival infection with *C. trachomatis* and other bacteria may promote ongoing inflammation and progressive scarring.[8,15,17] However, one RCT of

adjunctive azithromycin treatment following surgery in an environment with a low prevalence of trachoma found that treatment did not improve the outcome, and until more evidence is available from other settings the administration of additional azithromycin at surgery should not be routinely adopted.[8]

Given the disappointingly high rates of recurrence there is a pressing need to develop strategies to improve the long-term outcome of surgery to ensure that surgical services most effectively minimize the incidence of blindness caused by trachoma.

Fig. 2. **Number of patients undergoing trichiasis surgery since launch of the GET 2020.[a] (Data for 2005 are provisional)**



[a] GET 2020 = Global Alliance for the Elimination of Blinding Trachoma by 2020.

Source: International Trachoma Initiative country reports.

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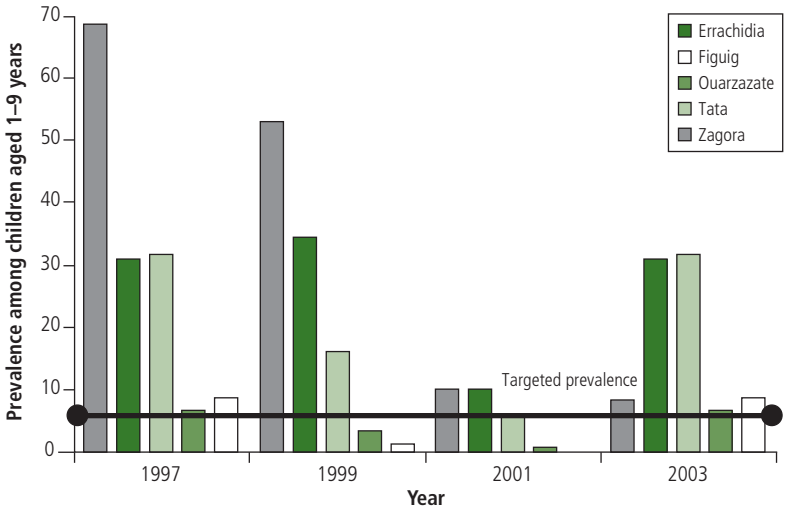
Antibiotics

A Cochrane review of the effect of antibiotics on trachoma showed that although antibiotics seem to lower the relative risk both of disease and infection at three months and 12 months after treatment, data are also consistent with the conclusion that antibiotics have no effect on an individual case.[18]

However, trachoma control programmes use antibiotics for two reasons: first, to treat individual infections (and thereby hopefully reduce each patient's risk of developing pathologically significant conjunctival scarring), and, second, to limit transmission of infection to others. Because many people who are infected do not have signs of disease on examination,[19] mass treatment of all individuals living in a community seems a rational approach wherever the prevalence of trachoma is high. Supervised mass treatment with topical tetracycline of populations in trachoma-endemic areas is logistically difficult since tetracycline must be applied twice a day for many weeks to be effective. Unsupervised treatment is believed to be ineffective because adherence to the treatment regimen is often poor.[20] For these reasons, the discovery that single-dose oral azithromycin was as effective for an individual case as supervised topical tetracycline[3] represented a significant breakthrough.

Fig. 3. **Impact of 7 years of the SAFE strategy on prevalence of grade TF[a] trachoma in children aged 1–9 years in five endemic provinces in Morocco**



Source: National coordinator of the Moroccan National Eye Care Programme.

[a] Prevalence of >10% trachomatous inflammation, follicular.

WHO 06.95

Subsequently, the "azithromycin in control of trachoma" trial was undertaken to compare the impact of azithromycin with tetracycline when given to whole communities.[21] Pairs of villages in the Gambia, Egypt and the United Republic of Tanzania were matched according to the prevalence of active trachoma among children. For both treatments village-wide prevalences of infection at one year were substantially lower than at baseline. The reduction in infection prevalence was greater with azithromycin than with tetracycline, although the difference was not significant.[21]

This study established the efficacy[21] and safety[22] of mass treatment with azithromycin. It was the basis for the launch of the Pfizer donation programme, and it invigorated the GET 2020 alliance. A mathematical model of the effect of periodic antibiotic treatment on clinical signs of disease predicted that to eliminate trachoma, mass treatment would be needed at least every six months in hyper-endemic areas and at least every 12 months in meso-endemic areas;[23] longitudinal data were needed to confirm or modify the treatment recommendations that were based on these findings and routinely used by national programmes.

Several studies have used quantitative polymerase chain reaction to study the epidemiology of ocular *C. trachomatis* infection in untreated communities and to provide empirical evidence of the impact of mass treatment with azithromycin. These studies have shown that:

- children who are younger than 10 years and individuals with intense inflammatory trachoma have the highest ocular loads of *C. trachomatis*, suggesting that the success of antibiotic distribution efforts might depend quite heavily on the coverage achieved in these groups;[24]
- in hypo-endemic and meso-endemic communities high coverage of treatment can reduce or interrupt transmission of ocular *C. trachomatis* for at least 17 months;[25,26]
- in hyper-endemic communities prevalence and intensity of infection may begin to rise about 12 months after a fall induced by mass treatment;[27] and
- the presence of a higher-than-median post-treatment load of ocular *C. trachomatis* predicts the likelihood of transmission of infection to family members.[27]

Additionally, these studies have underlined the poor correlation between signs of active disease and presence of infection (measured quantitatively), particularly after antibiotic treatment, where the prevalence of TF in children may remain persistently above 10% (mandating ongoing annual antibiotic distribution) for months or years after infection has virtually disappeared from the community.[26]

This last point presents a particular difficulty for programme managers. While on the one hand azithromycin is well tolerated by recipients and donated by Pfizer, it is wasted treating non-existent infections when it could be directed towards those with actual infections, if they could be identified. A rapid low-cost field-based test for *C. trachomatis* would be extremely useful to help programmes determine which communities need to be offered antibiotics. Early trials of a candidate dipstick assay have shown promising results. Distributing the drug requires allocating resources that could be used in other ways; in Ethiopia an assessment of the utility of saving both costs and drug by determining whether ocular *C. trachomatis* can be eliminated from a community by treating only children is ongoing.

Box 1. **Why has the SAFE strategy been successful?**

- The strategy is clear and understandable
- Progress can be measured using the WHO-endorsed simplified grading system to measure trachoma prevalence; this allows comparisons between and within countries
- Regular meetings allow for the exchange of information between programme managers and produce pride in achievements
- Regular meetings between operational researchers and programme managers encourage rapid uptake of new techniques and practices
- Delivery of services (such as eyelid surgery for trichiasis, distribution of antibiotics, latrine promotion) is performed effectively and inexpensively by non-specialists
- The success of each component of the strategy encourages communities to buy-in to other components
- Mass treatment with single-dose oral azithromycin is effective and feasible, and popular with recipient communities
- Azithromycin is well tolerated, relatively free from side-effects and has additional benefits such as being effective against malaria as well as infections of the respiratory tract and skin
- Resistance to azithromycin has not been reported for *C. trachomatis*
- Azithromycin is donated and shipped to endemic countries by Pfizer
- Advocacy for trachoma control by nongovernmental development organizations and WHO has led to increased governmental commitment in some countries
- Nongovernmental development organizations have had strong involvement in trachoma control
- Intersectoral programmes include organizations working on improving water supplies and sanitation in addition to those providing eye care

Facial cleanliness and environmental improvement

The "F" and "E" components of the SAFE strategy (facial cleanliness and environmental improvement) are frequently described together since their primary function is to prevent transmission rather than treat trichiasis or infection.[28] A series of risk-factor analyses found an association between not having a clean face and an increased individual likelihood of having signs of active trachoma, suggesting that face-washing could reduce the prevalence of trachoma.[29–31] Formative research in the United Republic of Tanzania suggested that it would indeed be possible to change hygiene practices to increase facial cleanliness and also demonstrated that it was possible to wash many faces with just a small quantity of water.[32, 33] A study in the Gambia showed that members of households that allocated a greater proportion of their water to hygiene had a reduced risk of trachoma compared with those who did not, thus providing additional support to the argument for promoting face-washing to control trachoma.[34] This evidence led to an RCT of hygiene promotion to control trachoma[35] that — although some of the comparisons narrowly failed to achieve statistical significance — was considered sufficiently compelling by WHO to warrant inclusion as part of the integrated strategy.

Eye-seeking flies have been associated with trachoma for hundreds of years,[28] but fly-control was not incorporated into national trachoma plans because there was no evidence that investment in it would have an impact on trachoma transmission. A series of small studies conducted in the Gambia suggested that eye-seeking flies were transmitting trachoma and also identified a putative vector, *Musca sorbens*, that breeds in human faeces.[36–38] A larger cluster-randomized controlled trial that tested both fly control with insecticide and the provision of household latrines to reduce the breeding media of *M. sorbens* in villages confirmed that *M. sorbens* was a trachoma vector and demonstrated that providing household latrines significantly reduced contact between flies and eyes.[39] The agency that provided the latrines was the same government department that had responsibility for rural sanitation. Participation in the operational research dovetailed with its own targets for latrine provision and helped it exceed its yearly goal. In common with trials of surgery delivery, the active participation of the implementing agencies as equal partners in the operational research ensured that there was no lag in putting research into practise and minimizing the "know–do" gap. Thus, the operational research became a part of practice.

There have been no RCTs studying the effect of providing water on the prevalence of trachoma, but several studies have shown that families living

further from a water source are at greater risk of trachoma than similar families living closer.[40–42] Trachoma has also been shown to disappear where water has become available, even in the absence of an antibiotic-based control programme.[43, 44] Provision of water sources is a component of a few national programmes, such as that in Morocco, but the perceived high cost makes it unattainable for most. Improving access to safe drinking water is included in Millennium Development Goal 7,[45] and national programmes are using this goal to ensure that water provision is prioritized for communities where trachoma is endemic.

No trachoma control programme in the world is based solely either on hygiene promotion or environmental change, but operational researchers must investigate their effects individually in order to unequivocally demonstrate efficacy. This necessitates recruiting several communities into trials because the interventions act at the level of the community and not the individual. Cost considerations usually limit the number of communities included in these studies to the minimum allowable, which inevitably leads to studies that have low statistical power to demonstrate an effect in excess of 30% against the comparison group. In the future, trials of face-washing and the provision of latrines should probably be repeated using the quantified load of *C. trachomatis* to determine the scale of the effect with greater precision.

Conclusions

Researchers working on trachoma in the past decade in Ethiopia, the Gambia, Nepal, the United Republic of Tanzania and other endemic countries have worked closely with national eye-care programmes. Thus, results are available to the programmes as soon as they are generated. A strong international network of personal contacts between those working on trachoma control has developed as a result of meetings of the GET 2020 alliance, the Carter Center programme reviews, and through informal contacts developed through the International Agency for the Prevention of Blindness and the International Centre for Eye Health. A number of national and regional programme managers have taken courses in community ophthalmology at the International Centre for Eye Health. The centre itself was supported by the International Trachoma Initiative to undertake an independent evaluation of trachoma control programmes in eight countries. These evaluations used a common methodology, developed at a workshop attended by stakeholders from each country, and were conducted in collaboration with national programmes by an international team including experts from other endemic countries in the region. Important lessons were learned and disseminated to programme managers in other countries.[46]

National programmes reporting at regional and international meetings inspire other programme managers, resulting in the rapid adoption of new approaches. For example, at least nine national trachoma control programmes reported progress towards increasing access to latrines at the GET 2020 meeting in 2003,[4] even though the peer-reviewed paper demonstrating the association between latrine provision and reduced contact between flies and eyes was not published until the following year. Similarly, the use of paramedical staff to perform eyelid surgery was rapidly and widely adopted, and the fear that programmes were offering a reduced-quality service was put to rest by independent assessment of the outcome of surgeries, comparing those performed by ophthalmologists with those performed by paramedical staff.

In the future it is likely that national policy on the use of azithromycin will be modified in light of results from studies on the rational use of antibiotics. As the prevalence of signs of trachoma declines, the decision to offer antibiotics may depend on the use of a point-of-care dipstick to detect whether ocular *C. trachomatis* is present in the community.

Combining operational research about trachoma with the implementation of the SAFE strategy offers an example of how to minimize the gap between knowledge and practise and how to put the results of research into policy and planning. ■

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Résumé

Stratégie SAFE de lutte contre le trachome : utilisation de la recherche opérationnelle pour planifier et mettre en œuvre des stratégies

Le trachome est une maladie négligée, mais en même temps la première cause infectieuse de cécité dans le monde. Cette maladie est source de pauvreté, de dépendance et d'obstacles au développement. Pour la combattre, on met en œuvre une stratégie approuvée par l'OMS (connue sous le sigle SAFE) et comprenant quatre axes d'intervention : chirurgie de l'entropion trichiasis, traitement antibiotique, nettoyage du visage et changement de l'environnement. Cette stratégie repose sur les éléments fournis par les essais de terrain. Elle est affinée en permanence grâce aux données de la recherche opérationnelle qui étayent les politiques et la planification à l'échelle nationale. Elle a influé à la fois sur les modalités d'administration et de mise en œuvre des programmes. Les résultats de cette recherche ont conduit aux évolutions suivantes : Il est fréquent maintenant que les actes chirurgicaux soient pratiqués par des agents paramédicaux appartenant à la communauté, plutôt que par des ophtalmologistes en milieu hospitalier; la distribution massive pendant un an d'une dose orale unique d'azithromycine a remplacé l'administration de la tétracycline par voie topique et on recourt à la promotion d'une meilleure hygiène, du lavage facial et de l'utilisation des latrines pour réduire la transmission. Les responsables de la mise en œuvre des programmes sont partenaires à niveau égal de la conduite de la recherche opérationnelle, ce qui diminue le fossé entre savoir et faire et le décalage fréquent entre la réalisation

des essais et la mise en pratique de leurs résultats. La recherche opérationnelle est maintenant intégrée à la pratique. S'il reste encore beaucoup de questions sans réponse, les coordinateurs de programmes nationaux peuvent raisonnablement espérer que les programmes de lutte contre le trachome reposant sur la stratégie SAFE donnent de bons résultats.

Resumen

Estrategia SAFE de control del tracoma: uso de las investigaciones operacionales para la formulación de políticas, la planificación y la implementación

El tracoma es una enfermedad desatendida y la principal causa infecciosa de ceguera a nivel mundial. Provoca miseria y dependencia y constituye un obstáculo para el desarrollo. El tracoma está siendo combatido mediante una estrategia integrada apoyada por la OMS que combina la corrección quirúrgica de la triquiasis, la antibioticoterapia, la higiene facial y las mejoras ambientales (en sus siglas inglesas: SAFE). Esta estrategia, basada en la evidencia obtenida en ensayos sobre el terreno y objeto de continuas mejoras gracias a investigaciones operacionales que orientan las políticas y la planificación nacionales, ha influido en la ejecución de los programas. Como consecuencia de los resultados de las investigaciones operacionales, las intervenciones quirúrgicas son realizadas a menudo por personal paramédico en las comunidades, más que por oftalmólogos en los hospitales; la distribución masiva anual de una sola dosis oral de azitromicina ha reemplazado al uso tópico de tetraciclina; y para reducir la transmisión se fomenta una mayor higiene, el lavado de la cara y el uso de letrinas. Los responsables de la implementación de programas han participado como asociados en condiciones de igualdad en la realización de las investigaciones operacionales, mitigando así la brecha teórico-práctica y reduciendo al mínimo el frecuente desfase entre la finalización de los ensayos y la puesta en práctica de sus resultados. Las investigaciones operacionales se han convertido en parte de la práctica. Aunque quedan todavía muchas preguntas sin respuesta, la confianza de los coordinadores de los programas nacionales en que los programas de control del tracoma basados en la estrategia SAFE funcionarán es una expectativa razonable.

ملخص

استـراتيجية SAFE لمكافحة التراخوما: استخدام البحوث الميدانية من أجل التنفيذ والسياسات والتخطيط

إن التراخوما من الأمراض المهملة، وهو السبب الرئيسي العدوائي للعمى، ويؤدي للبؤس والاتكال، ويمثِّل عقبة تعترض سبيل التنمية. وتكافح منظمة الصحة العالمية التراخوما باستـراتيجيتها المتكاملة بجراحة الشعرة والمعالجة بالمضادات الحيوية وبتنظيف الوجه وتحسين البيئة، وهي استـراتيجية تعرف بـالاسم المختصر SAFE. وتستند هذه الاستـراتيجية على بينات من التجارب الميدانية، وتتحسّن بالبحوث الميدانية التي تقدم المعلومات للسياسات والتخطيط على الصعيد الوطني، وتؤثِّر هذه الاستـراتيجية على إيتاء وتنفيذ البرامج. واستناداً للموجودات التي تمخضت عنها البحوث الميدانية أصبحت الجراحة تجري في غالب الأحيان من قِبَل المساعدين الطبيـين في المجتمعات وليس من قِبَل أطباء العيون في المستشفيات، كما حلّ التوزيع الجموعي السنوي لجرعة وحيدة من الأزيثرومايسين محل التتـراسيكلين الموضعي، كما يفيد غسل الوجه واستخدام المراحيض وتعزيز النظافة الشخصية لإنقاص السراية. وقد أصبح المساهمون في تنفيذ البرامج شركاء لهم نفس الأهمية في تنفيذ البحوث الميدانية، مما أنقص الفجوة في المهارات وخفّف من مدى التأخر الذي يتلو استكمال البحوث ويفصل بينها وبين وضع النتائج موضع الاستعمال. وهكذا أصبحت البحوث الميدانية جزءاً من الممارسة، ورغم وجود الكثير من الأسئلة بدون أجوبة، فإن لدى المنسِّقين للبرامج توقعات معقولة بنجاح البرامج المستندة على استـراتيجية SAFE في مكافحة التـراخوما.

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