Village-integrated eye workers for prevention of corneal ulcers in Nepal (VIEW study): a cluster-randomised controlled trial

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Summary

Background Corneal ulcers are a common cause of blindness in low-income and middle-income countries, usually resulting from traumatic corneal abrasions during agricultural work. Antimicrobial prophylaxis of corneal abrasions can help prevent corneal ulcers, but delays in the initiation of therapy are frequent. We aimed to assess whether a community-based programme for corneal ulcer prevention would reduce the incidence of corneal ulceration.

Methods A cluster-randomised trial was performed in village development committees (VDCs) in Nepal. VDCs in the catchment area of Bharatpur Eye Hospital, Nepal with less than 15 000 people were eligible for inclusion. We randomly assigned (1:1) VDCs to either an intervention group or a control group. In the intervention VDCs, existing female community health volunteers (FCHVs) were trained to diagnose corneal abrasions and provide a 3-day course of ophthalmic antimicrobials to their patients. In the control VDCs, FCHVs did not provide this intervention. Participants were not masked given the nature of the intervention. Both groups were followed up for 3 years for photographic evidence of corneal ulceration. The primary outcome was the incidence of corneal ulceration, determined by masked assessment of corneal photographs. The analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, NCT01969786.

Findings We assessed 112 VDCs, of which 24 were enrolled. The study was performed between Feb 4, 2014, and Oct 20, 2017. 12 VDCs were randomly assigned to the intervention group and 12 to the control group. 252 539 individuals were included in the study (130 579 in the intervention group and 121 960 in the control group). FCHVs diagnosed and provided antimicrobials for 4777 corneal abrasions. The census identified 289 corneal ulcers among 246 893 person-years in the intervention group (incidence 1·21 cases [95% CI 0·85–1·74] per 1000 person-years) and 262 corneal ulcers among 239 170 person-years in the control group (incidence 1·18 cases [0·82–1·70] per 1000 person-years; incidence rate ratio 1·03 [95% CI 0·63–1·67]; p=0·93). Medication allergy was self-reported in 0·2% of participants.

Interpretation We did not detect a reduction in the incidence of corneal ulceration during the first 3 years of a community-based corneal ulcer prevention programme. Further study might be warranted in more rural areas where basic eye care facilities are not available.

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Introduction

Corneal opacity is an important cause of blindness globally.[1] As traditional infectious causes of corneal opacity like trachoma and onchocerciasis have declined, the importance of corneal ulceration (ie, microbial keratitis) has increased.[1,2] In low-income and middle-income countries, the most common cause of a corneal ulcer is traumatic corneal abrasion, which is often caused during agricultural work or other manual labour.[3–9] In these settings, seeking care for ocular trauma is often delayed, if pursued at all, increasing the likelihood of developing a corneal ulcer and a subsequent vision-threatening corneal opacity.[3,8]

Earlier initiation of antimicrobial prophylaxis for corneal abrasions might be an effective way to reduce the burden of corneal infections in resource-limited settings.[10] For example, a previous study of patients with corneal abrasions in Nepal found that corneal ulcers were more likely to develop if antimicrobial therapy was delayed by more than 18 h after the inciting trauma.[11] Several studies in southeast Asia have attempted to reduce the time from trauma to treatment by instituting programmes in which community health workers identify cases of ocular trauma or corneal abrasion and provide antimicrobial prophylaxis directly or through referral.[11–15] These studies had promising results, with very few corneal ulcers detected after programme implementation; however, none of the studies included an untreated control group, so it was not possible to determine whether the paucity of ulcers

Research in context

Evidence before this study

We searched PubMed from inception until Dec 1, 2021, for studies published in English, using the search terms "cornea*[Title] AND ulcer*[Title] OR opacit*[Title] AND prevent*[Title]". Observational studies of community health volunteer programmes for corneal ulcer prevention performed in several settings in southeast Asia found very low rates of corneal ulceration, and a randomised trial in India comparing antibiotic versus antifungal prophylaxis found very low rates of corneal ulceration in both groups. However, the low rate of corneal ulcers in these studies prevented an assessment of the effectiveness of the programmes relative to the absence of a programme.

Added value of this study

The Village-Integrated Eye Worker trial was a cluster-randomised trial in which existing female community health volunteers in intervention communities were trained to diagnose corneal abrasions and provide prophylaxis with topical antibiotics and antifungals. Control communities received no intervention. A census with corneal photography was performed each year during the 3-year trial, and incident corneal ulcers were determined by photo-graders masked to intervention allocation. Ultimately, the rate of corneal ulceration was similar in the two groups, although subgroup analyses found that the intervention might be more effective in areas that were more rural and remote. Strengths of the study include its large size, long duration, and masked outcome assessment, as well as its setting in an area with a relatively high incidence of corneal ulceration.

Implications of all the available evidence

Community health volunteer programmes are a promising intervention for corneal ulcer prevention, but such programmes might not be effective in all settings and the effectiveness might depend on socioeconomic development and availability of health facilities. Further study of similar interventions should be targeted to rural and remote communities with poor access to basic health services.

was caused by the programme or by other factors. To address this key limitation, a cluster-randomised trial was designed to test the effectiveness of a community-based programme for corneal ulcer prevention relative to an untreated control group. The cluster-randomised design was appropriate for the community based nature of the intervention and reduced the risk of contamination compared with an individually-randomised trial. The trial tested the hypothesis that introducing a community health volunteer programme for the quick diagnosis and management of corneal abrasions would ultimately reduce the cluster-level incidence of corneal ulcers.

Methods

Study design and participants

The Village-Integrated Eye Worker (VIEW) trial was a cluster-randomised trial performed from Feb 4, 2014, to Oct 20, 2017, in the Chitwan and Nawalparasi districts of Nepal. Study clusters were government-defined administrative units known as village development committees (VDCs), which were randomised to receive a corneal ulcer prevention programme or to no programme and followed up for 3 years for photographic evidence of corneal ulceration. The design and methods of the VIEW trial have been reported elsewhere.[16] Ethics approval for the trial was obtained from the University of California San Francisco Committee on Human Research, Nepal Netra Jyoti Sangh, and the Nepal Health Research Council. A Data and Safety Monitoring Committee reviewed the protocol before study implementation and provided oversight during the trial. The trial adhered to the tenets of the Declaration of Helsinki.

The study was set in a low-lying, agrarian, relatively densely populated part of Nepal; approximately three-quarters of the population was literate in the 2011 national census.[17] VDCs were administrative divisions in existence at the start of the study; each VDC consisted of nine wards. Each ward had a government-supported female community health volunteer (FCHV) elected by the community to perform public health tasks (eg, family planning and nutrition education for pregnant women). VIEW leveraged the FCHV programme, adding eye care to their portfolio of services.

Because the intervention was thought likely to be most effective in rural areas, VDCs in the catchment area of Bharatpur Eye Hospital with a population of less than 15 000 on the 2001 Nepal census were deemed eligible. Residents of all ages, from all households in the study communities were offered enrolment through an annual door-to-door census by census workers. Participants were eligible if they were residing in the catchment area at the time of the census. Verbal informed consent was obtained for census activities before randomisation was performed. Written informed consent was obtained for the FCHV intervention after randomisation was completed.

Randomisation and masking

VDCs were stratified by district (ie, Chitwan *vs* Nawalparasi; appendix p5) and randomly assigned (1:1) to receive the intervention (FCHV corneal ulcer prevention programme) or no intervention (control group). The study biostatistician used R Project for Statistical Computing, version 3 (Vienna, Austria) to generate the random allocation sequence after the baseline census was

completed. Allocation was concealed by enrolling all VDCs before randomisation and by offering the prevention programme to all community members in the intervention VDCs simultaneously. Study staff at the Bharatpur Eye Hospital implemented the randomisation sequence.

Given the nature of this community-based intervention, study participants and the study personnel administering the intervention were not masked. However, census workers were not informed of the randomisation allocation and all publicity materials (eg, posters) were removed during census periods to avoid unmasking census workers. Outcome assessors (ie, photo-graders) were masked to intervention allocation. Contamination was possible since people travelling from control VDCs to intervention VDCs could have seen publicity materials, although the large size of the VDCs limited the magnitude of contamination, and intervention FCHVs only offered eye services to people living in the intervention VDCs.

Procedures

A publicity campaign was conducted in intervention VDCs to encourage residents to present to FCHVs within 24 h of experiencing ocular trauma (ie, any injury to the eye or eyelid, typically accompanied by pain, tearing, and blurred vision). Publicity activities included orientation meetings with local leaders and community groups, door-to-door visits by FCHVs, and the distribution of posters, pamphlets, calendars, and pens.

In intervention VDCs, existing FCHVs were trained to diagnose corneal abrasions using fluorescein strips, 2·5 times magnifying loupes, and an ultraviolet flashlight. FCHVs in the control VDCs did not receive this training. If a corneal abrasion was diagnosed, the FCHV provided 1% chloramphenicol ointment in single-dose applicaps (Chloromycetin Kaps, Pfizer India) and 1% itraconazole ointment (Itral, Jawa Pharmaceuticals India), each to be applied three times a day for 3 days. Pregnant women or those with a self-reported chloramphenicol allergy received 1% azithromycin ointment (Zaha, Ajanta Pharma India) three times a day for 3 days instead of chloramphenicol. Chloramphenicol was chosen on the basis of its efficacy and safety in previous community-based studies of corneal ulcer prophylaxis[11–14] and because the formulation as an ointment provides a better barrier to infection relative to an eyedrop. The packaging as single-dose applicaps aided in determining adherence, and the high concentrations achievable with a topical preparation of this broad-spectrum antibiotic were likely to be effective for most gram-positive and many gram-negative organisms. Itraconazole was chosen because of its availability as an ointment and its relatively low cost. Together, these two medications cover the majority of pathogens that cause infectious keratitis in Nepal.[18–23] The FCHV administered the first dose of the antimicrobial ointments. Participants were asked to return to the FCHV for a follow-up examination after 3 days, at which point the FCHV re-examined the affected eye with fluorescein and asked an open-ended question about adverse events. FCHVs recorded participant information on paper forms. Any participant with a corneal ulcer, bilateral corneal abrasions, visual acuity worse than Counting Fingers in the non-affected eye, or another referable eye problem at the initial visit was referred to Bharatpur Eye Hospital or the nearest primary eye care centre. Participants with a corneal ulcer, non-healing corneal abrasion, or allergic reaction at the follow-up visit were also referred. FCHVs obtained written informed consent from all participants. Because the goal of the research was to assess the effectiveness of a community-based corneal ulcer prevention programme versus no programme, the control communities did not receive any study interventions. A group of six study supervisors performed periodic home visits and held monthly refresher training for the remainder of the study, focusing on review of examination procedures and assessment of ophthalmic knowledge through a set of photographs of corneal abrasions and ulcers.

Starting 3 months after randomisation, and then annually, an intervention awareness survey (a random sample of 15 households per ward was selected) was conducted in intervention and control VDCs by survey workers who were masked to the intervention allocation. A random sample of households was selected from the previous census to participate in the survey, and they were visited by trained survey workers who asked an adult in each selected household a series of questions to determine their level of awareness of the intervention. Respondents were asked an open-ended question about their preferred provider for eye trauma. In the second two annual surveys the respondent was additionally asked in a closed-ended question to list all the providers, including the FCHVs, who were available to manage eye trauma. The survey provided information on the effectiveness of the publicity campaign in intervention VDCs, as well as the level of contamination to control VDCs.

A door-to-door census was started at months 0, 12, 24, and 36 in all study VDCs to enrol participants and perform corneal photography. Each census was conducted during the calendar year of the study (ie, 2014–17), with an initial pass of households taking several months, and subsequent follow-up activities to increase photographic coverage for the remainder of the year. Trained census workers visited all households in the study VDCs at each census. At follow-up censuses, all household members were asked a series of screening questions for eye trauma (eg, eye injury, sudden decreased vision, eye pain, and eye infection) occurring since the previous census. An attempt was made to elicit information from the household member themselves, but guardians were allowed to provide data for household members not able to respond (eg, children). Data were collected on mobile

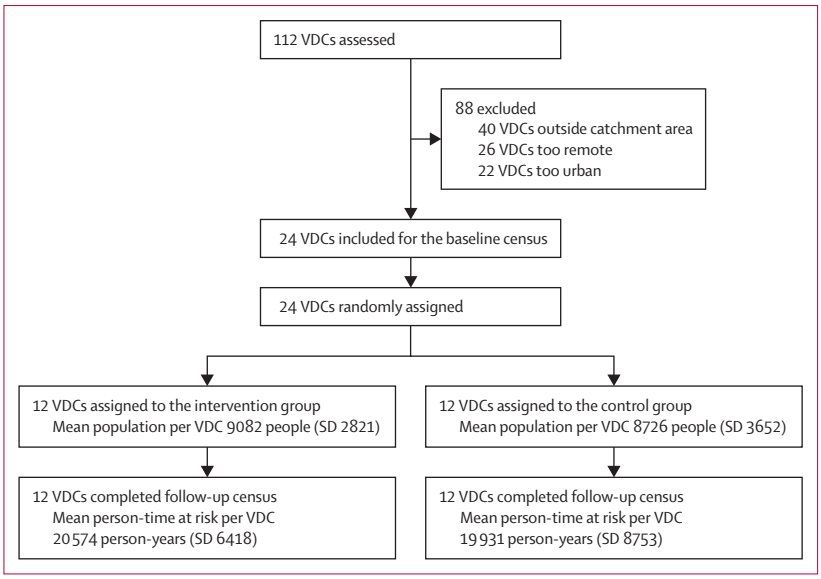

Figure 1: **Trial profile**
VDC=village development committee.

devices using a custom-designed mobile application (Conexus, Los Gatos, CA, USA). Corneal photographs were taken using the Corneal CellScope (Development Impact Lab, Berkeley, CA, USA), a custom-made 3D-printed smartphone attachment with a +25 dioptre lens and external illumination. Photographs were taken of both eyes of all residents at the baseline and final censuses, and of both eyes of residents answering positively to one of the eye trauma screening questions during interim censuses.

Photographs were graded for evidence of incident corneal ulceration by trained graders, masked to the intervention allocation. For study purposes incident corneal ulceration was defined as evidence of an active corneal ulcer or a new opacity not present at a previous census. All photographs taken of an eye during a census were presented together, and grades were assigned to the eye. Photographs from individuals who answered any screening questions about eye trauma positively at a follow-up census were presented to two trained graders in a random order, without identifying information. Sets of photographs were presented for each eye and each census separately, and they were graded for corneal ulceration on a 4-category ordinal scale (eg, definitely yes, probably, possibly, and definitely no). If the photograph of the eye was graded as having possible, probable, or definite evidence of corneal ulceration (eg, either an active ulcer or an opacity) then all photographs from previous censuses were displayed to determine whether the corneal pathology had developed since the previous photograph. If photographs from a previous phase were of a different eye, this was noted. All photographs graded as possible, probable, or definite corneal ulceration were subsequently graded by one of three cornea specialists using the same procedures. An eye was classified as an incident corneal ulcer if the cornea specialist graded definite or probable corneal ulceration at one census, and possible or no ulceration in the same eye at a previous census.

For the **manual of procedures** see https://osf.io/t5wp4/

For the **statistical analysis plan** see https://osf.io/rmezw/

Outcomes

The primary outcome was incidence of corneal ulceration, assessed from masked grading of corneal photographs taken at each census. Individuals were allowed to contribute multiple incident ulcers over the study but could contribute no more than one new incident ulcer per eye per census period. Pre-specified secondary outcomes were the prevalence of visual impairment caused by incident corneal ulceration and the cost-effectiveness of the intervention (each to be reported in a separate publication) as well as the fidelity indicators of time from eye trauma to FCHV presentation (intervention group only) and awareness of study intervention (both groups).

Statistical analysis

We estimated that including 12 VDCs per group would provide greater than 80% power to detect a 30% reduction in the incidence of corneal ulcers at an α of 0·05. This calculation assumed 9000 individuals per cluster (VDC) based on average VDC size in the study area, an annual incidence in the control group of 100 cases per 100 000 person-years based on previous studies, an intra-class correlation coefficient (ICC) of 0·00015, and 3 years of follow-up.[24]

The primary intention-to-treat analysis employed negative binomial regression on VDC-level data to model the count of incident corneal ulcers during the entire study period as a function of treatment group, with log person time-at-risk as an offset. For the time-at-risk, individuals began contributing person-time at the first census in which they had photographs taken and continued to contribute time until their final census visit. Participants were censored if documented as having died or moved on the census, or at the final census visit (36 months), whichever occurred first. Individuals with incident corneal ulcers continued to contribute person-time since they remained at risk for additional ulcers. The model's dispersion parameter accounted for the clustered nature of the data. Significance testing was performed by Monte Carlo permutation (n=10 000 replications, accounting for stratified randomisation), with an overall α of 0·05 for the interim and final analyses. The pre-planned interim analysis was performed after the first follow-up census; this analysis spent 0·001 α and did not meet pre-specified criteria for stopping early. Exploratory subgroup analyses were performed using similar regression models, but on ward-level data. Analyses were performed in R (version 4). The manual of procedures and statistical analysis plan are available.

	Intervention VDC group (n=12)	Control VDC group (n=12)
Number of wards*		
Urban	0·9 (2·3)	0·6 (2·0)
Peri-urban	6·8 (2·9)	6·8 (3·6)
Rural	1·3 (2·2)	1·6 (3·1)
Population	9082·0 (2821·0)	8726·0 (3652·0)
Proportion female	57% (2·0)	56% (2·0)
Age distribution		
0–19 years	41% (4·0)	41% (4·0)
20–39 years	30% (2·0)	31% (2·0)
40–59 years	19% (2·0)	19% (2·0)
≥60 years	10% (1·0)	10% (1·0)
Proportion photographed	85% (9·0)	85% (12·0)

Data are mean (SD) per community among the 12 VDCs in each group. VDC=village development committee. *Each VDC in the study area was comprised of nine wards. Wards were classified as urban, peri-urban, or rural for internal study purposes by local study staff who visited communities as part of the study and were masked to study results. Classification was on the basis of a synthesis of numerous factors, including the geography (plains *vs* hills); access to transport; distance from the nearest large city, government offices, hospital, and main highway; and government designation as rural or urban.

Table 1: **Baseline characteristics of 24 VDCs enrolled in the trial**

The study was registered on ClinicalTrials.gov, NCT01969786, and it was overseen by a Data and Safety Monitoring Committee.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The initial census started on Feb 4, 2014, and enumerated 213 697 people. 24 VDCs met inclusion criteria and were included in the trial. Randomisation was performed on May 22, 2014, with 12 VDCs allocated to the control group and 12 VDCs to the intervention group (figure 1). Baseline characteristics of the intervention and control VDCs were well balanced (table 1).

In June 2014, 116 FCHVs from the 12 intervention VDCs were trained to diagnose corneal abrasions and provide antimicrobial ointments as prophylaxis. The mean attendance at the monthly refresher trainings across all sessions of the study period was 91% (95% CI 88–95). FCHV services were publicised through written materials posted throughout the community and by word of mouth.[16] An annual survey performed on a random sample of 15 households per ward found a marked increase in awareness of the FCHV programme over the 3 years of the study (figure 2). In the final study year, 25% (95% CI 13–37) of respondents in the intervention group said their FCHV was their provider of choice for ocular trauma and 40% (27–57) were aware that the FCHV provided services for ocular trauma, compared

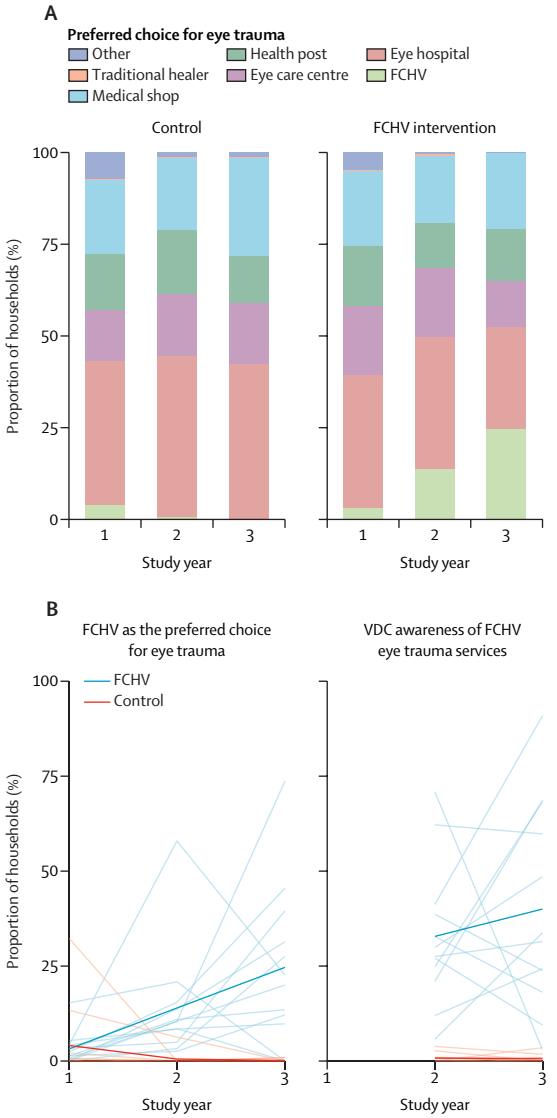

Figure 2: **Intervention awareness survey**

FCHV=female community health volunteer.VDC=village development committee. Starting three months after randomisation, and then annually, a random sample of households in each VDC was surveyed. A member of the household was asked an open-ended question about where they would go if they experienced eye trauma, and their preferred provider was recorded. In the second and third annual surveys, the respondent was asked about all the providers available for eye trauma, regardless of whether it was their preferred provider. Panel A shows the distribution of responses for the preferred provider of eye care across each annual survey, with all villages aggregated. In panel B, each thin line depicts a single VDC over time. The thick line depicts the mean.

with 0·2% (0–0·4%) and 0·6% (0·1–1·4%) of the control group, respectively.

Over the 3-year study period, FCHVs completed 10 363 initial patient visits, of which 6411 (61·9%) were due to ocular trauma and 4777 (46·1%) were diagnosed with a corneal abrasion. Ophthalmic antimicrobials were provided for all cases of corneal abrasion. Self-reported adherence to prophylactic antimicrobial therapy was very

	Intervention VDCs (n=12)*
FCHV visits due to eye trauma	534 (182·0)
Female	60% (5·0)
<20 years	22% (4·0)
20–39 years	35% (3·0)
40–59 years	33% (3·0)
≥60 years	10% (2·0)
Presenting within 18 h	59% (6·0)
Presenting within 24 h	72% (5·0)
FCHV-diagnosed corneal abrasion†	398 (189·0)
Completing 4-day follow-up	96% (3·0)
Completing antimicrobial prophylaxis‡	95% (3·0)
Self-reporting allergy to antimicrobial	0·2% (0·2)
Referred to eye hospital§	4% (2·0)
Abrasion healed at 4 days†	94% (3·0)
Abrasion not healed at 4 days†	2% (1·0)
Abrasion status at 4 days unknown¶	4% (4·0)

Data are mean (SD). VDC=village development committee. FCHV=female community health volunteer. *Mean per community among the 12 intervention VDCs. †Corneal abrasions as observed by FCHV with fluorescein strips, ultraviolet flashlight, and loupes. ‡Completion of all doses of a 3-day course of three times a day antibiotic and antifungal, by self-report at 4-day follow-up. §Indications for referral included bilateral corneal abrasions, suspicion for a corneal ulcer, visual acuity worse than Counting Fingers in the unaffected eye, a non-healed abrasion at the 4-day follow-up visit, or another abnormality the FCHV could not diagnose. ¶4% of people were lost to follow-up.

Table 2: **Characteristics, adherence, and outcomes of individuals visiting FCHVs for eye trauma**

high, and the vast majority of abrasions had healed by the time of repeat examination by the FCHV (table 2). The number of corneal abrasions diagnosed by the FCHV more than doubled each year over the 3 years of the study (appendix p 6).

See Online for appendix

The number of residents from each VDC participating at each phase of the three follow-up censuses is summarised in the appendix (appendix p 3). A total of 130 579 individuals in the intervention group and 121 960 individuals in the control group were enrolled over the course of the study (ie, at baseline, 12 month, or 24 month census), of which 114 569 (87·7%) and 109 102 (89·5%) were eligible for inclusion in the primary outcome (ie, present and photographed at one census and present on at least one subsequent census). Of these, 17 287 people in the intervention group and 21 020 in the control group answered affirmatively to at least one eye trauma screening question at a follow-up census, of whom 16 961 (98·1%) and 20 540 (97·7%), respectively, had corneal photographs available from at least two censuses available for grading.

A total of 85 237 distinct sets of eye photographs from one of the three follow-up censuses were screened by two independent graders during a first round of photograding, of which 13 925 were sent to a cornea specialist for review because of a possible corneal ulcer. The vast majority of eyes had photographs that were judged to be of good (n=12 381; 88·9%) or acceptable (n=1375; 9·9%) quality, with only 169 (1·2%) sets of photographs deemed ungradable. A total of 289 incident corneal ulcers were discovered in the intervention group and 262 incident corneal ulcers in the control group during the 3 years of follow-up (appendix p 7). Annual incidence rates are shown for each VDC in the appendix (appendix p 4). The estimated incidence was 1·21 cases (95% CI 0·85–1·74) per 1000 person-years in the intervention group and 1·18 cases (0·82–1·70) per 1000 person-years in the control group (incidence rate ratio [IRR] 1·03 [95% CI 0·63–1·67]; permutation p=0·93; pre-specified primary analysis). Intra-cluster correlation of incident corneal ulceration was estimated as an ICC of binary person-level data in the control group (ANOVA-based ICC=0·001 [95% CI 0–0·003]). In exploratory subgroup analyses, wards that were more rural and remote tended to have fewer corneal ulcers in the presence of the intervention (table 3). For example, the incidence of corneal ulceration was lower in the intervention group than control group in wards classified by the hospital as rural (IRR 0·50 [95% CI 0·19–1·30]), but not in those classified as peri-urban or urban (IRR 1·31 [0·86–1·99]); or study group by subgroup interaction (p=0·04; appendix, p 8). The only reported adverse events were self-reported ocular allergic reactions, which occurred in eight of the 4777 participants who took the ophthalmic study medications (mean fraction per VDC 0·2% [95% CI 0·1–0·3]; table 2).

Discussion

Infectious keratitis frequently results in corneal scarring and subsequent vision loss, even when treated successfully with antimicrobial therapy;[25] thus, the most effective way to reduce corneal blindness might be to prevent the corneal ulcers from occurring.[2] The present trial assessed whether the incidence of corneal ulcers would be reduced by a community-based programme designed to promptly identify and provide antimicrobial prophylaxis for traumatic corneal abrasions. Despite evidence of intervention uptake and awareness, the VDCs randomised to the intervention continued to have similar levels of corneal ulceration as control VDCs. Exploratory analyses found a substantial difference in intervention effectiveness when considering geography, with greater effectiveness in more rural and remote areas.

Corneal abrasions due to eye trauma have been shown to be the most important risk factor for corneal ulcers in low-income and middle-income countries.[6] Corneal trauma removes the protective corneal epithelium, providing a route for bacterial or fungal infection. Corneal epithelial defects typically take 24–72 h to heal, and should be treated with topical antimicrobial prophylaxis until healing has occurred.[26] Delayed initiation of antimicrobial prophylaxis in a patient with a corneal abrasion is thought to be an important risk factor for the development of a corneal ulcer.[11] In the present

trial, 72% of people with eye trauma presented to an FCHV within 24 h, suggesting that for individuals who participated in the intervention, antimicrobial prophylaxis was started relatively promptly. It is difficult to know how many community members who developed a corneal abrasion did not present to the FCHV, and thus might have had a longer delay to antimicrobial prophylaxis or not received any treatment.

Many requirements would need to be met in order for the intervention to be effective. Perhaps most importantly, both the FCHVs and community members would need to trust in the programme. Community members would need to be aware the intervention existed, have confidence in the diagnostic abilities of the FCHV, and accept the antimicrobial therapy being offered. Community members would need to know where the FCHVs lived and walk or find transport. FCHVs would need to accept this new job responsibility—for which they were not paid—and demonstrate skill at diagnosis and organisation in maintaining their inventory of supplies and medications. FCHVs would also need to maintain their examination skills over time, since they could go weeks without seeing a patient. FCHVs would need to maintain their enthusiasm and willingness to participate in the programme over time. In addition, the medications themselves would need to be effective in preventing corneal infections when instilled in an eye with a corneal abrasion.

It is difficult to determine which factors were the most important for this trial's null result. FCHVs were quite engaged with the programme and received frequent visits from study supervisors, in addition to more formal annual training. Study staff helped FCHVs maintain their inventories of supplies and printed materials for publicity campaigns. However, it took a while to build awareness of the intervention, and awareness still had not reached peak by the time of the third annual household survey. It is possible that the intervention was not instituted for a long enough period of time for community members to be aware of the FCHV programme and trust the FCHV's diagnostic abilities and management skills. Although FCHV visits for abrasions increased substantially each year of the study, the intervention almost certainly continued to miss some community members, either because of a lack of awareness or because they preferred to seek care elsewhere. Furthermore, community members in the control VDCs might also have been receiving prompt treatment, either from a health-care professional or from a medical shop. A survey of medical shops in the study area found that antibiotics were recommended for most eye conditions, so it is possible that community members with corneal abrasions in the control communities were also receiving appropriate prophylaxis.[27]

An intriguing finding of this study—albeit in an exploratory, hypothesis-generating analysis—was the suggestion that the intervention might be more effective in rural and remote areas than in urban and peri-urban areas. We can speculate about the reasons such an intervention could be more effective in rural areas. Rural communities are farther from health-care providers and of lower economic means, thus they could have been more willing to accept the free services from the FCHV. In contrast, someone living in an urban area might have found it more convenient to visit a medical shop or clinic instead of co-ordinating with the FCHV. Individuals from rural communities might also have been more likely to sustain eye trauma during agricultural work, and thus might have had more opportunities to visit the FCHV.

This study had several limitations. A large geographical area was chosen as the randomisation unit in order to minimise contamination, but this limited the number of randomisation units for analysis, reducing the statistical power of the trial. The outcome of corneal ulceration was based on photography in order to enable a masked assessment. However, some otherwise eligible participants did not contribute data from photographs—either because photographs were not captured, or because the photographs were not of sufficient quality. In addition, although previous work has demonstrated

	Wards	Intervention corneal ulceration incidence rate, cases per 1000 person-years (95% CI)	Control corneal ulceration incidence rate, cases per 1000 person-years (95% CI)	Corneal ulceration incidence rate ratio (95% CI)	Interaction p values*
Elevation†					0·34
Low (<300 m)	168	1·16 (0·81–1·65)	0·98 (0·65–1·48)	1·17 (0·68–2·02)	..
High (≥300 m)	48	1·28 (0·95–1·73)	1·79 (0·77–4·12)	0·72 (0·30–1·75)	..
Population density‡					0·018
Above median	108	1·13 (0·78–1·63)	0·72 (0·51–1·01)	1·57 (0·95–2·60)	..
Below median	108	1·23 (0·95–1·59)	1·72 (1·01–2·92)	0·72 (0·40–1·29)	..
Distance from road§					0·037
Close (<3 km)	128	1·34 (0·90–1·98)	0·94 (0·69–1·28)	1·43 (0·87–2·36)	..
Far (≥3 km)	88	1·00 (0·70–1·42)	1·85 (0·85–4·05)	0·54 (0·23–1·28)	..
Hospital classification¶					0·044
Urban or peri-urban	182	1·15 (0·85–1·57)	0·88 (0·66–1·17)	1·31 (0·86–1·99)	..
Rural	34	1·43 (0·94–2·18)	2·88 (1·21–6·81)	0·50 (0·19–1·30)	..

Data are n or incidence rate (95% CI), unless otherwise specified. Study wards were stratified according to several criteria likely related to the rural-urban status of the community. The incidence of corneal ulceration is shown for each treatment group across each stratum, along with the incidence rate ratio for the stratum (ward-level analyses). *Interaction of study arm (intervention *vs* control) by subgroup in negative binomial regression of ward-level data with robust standard errors to account for village-level clustering. †Extracted with R package elevatr for each household using baseline global positioning system coordinates, summarised as a ward-level mean. Communities at higher elevation would be expected to be more rural. ‡Estimated for each household as the average distance to its ten nearest neighbours, using global positioning system data from the baseline census, summarised as a ward-level mean. Communities with a lower population density would be expected to be more rural. §Distance from the East–West highway, a major urbanised thoroughfare in Nepal. Estimated for each household using baseline global positioning system data; wards in which all households were within 3 km were classified as close, and the remaining as far. Communities farther from the road would be expected to be more rural. ¶Classified for internal study purposes based on the opinions of local study staff who visited communities as part of the study and were masked to study results.

Table 3: **Subgroup analyses**

high sensitivity and specificity of smartphone photography for detecting corneal opacities and several rounds of grading increased the precision of the outcome, photographs nonetheless still provide less information than a standard ophthalmologic examination, and could have been misclassified.[28] The study medications might have offered incomplete coverage, especially since *Pseudomonas* spp have intrinsic resistance to chloramphenicol, and itraconazole has poor efficacy for *Fusarium* spp.[29] However, *Pseudomonas* and *Fusarium* account for a small fraction of corneal ulcers in Nepal, and very few abrasions in the intervention arm did not heal after the 3-day course of study antimicrobials, suggesting that the medications chosen for the trial were sufficient for prophylaxis purposes.[18–23] Finally, as the study was performed in a specific area of Nepal, it is not clear whether the results can be generalised to other settings. Given the results of the exploratory analyses, further study in areas that are rural or remote could be worthwhile.

In summary, this trial was unable to demonstrate that the implementation of a community-based corneal ulcer prevention programme in Nepal reduced the incidence of corneal ulceration over 3 years, although exploratory subgroup analyses suggested the intervention could potentially be more effective in rural and remote communities. Awareness and participant responsiveness increased over the study period, suggesting that community-based programmes may need longer observation periods to determine effectiveness.

Contributors

JDK and KSO participated in study design, data acquisition, data management, data analysis, data interpretation, drafted the manuscript, verified the underlying data, and were responsible for the decision to submit the manuscript. RB and JAG participated in data acquisition and data interpretation. RPK, JPW, MS, and MU participated in study design, data acquisition, and data interpretation. BP participated in data acquisition and data management. TCP participated in study design, data management, data analysis, data interpretation, and performed randomisation. TML participated in study design, data acquisition, data analysis, and data interpretation. All authors had access to all the data in the study and revised and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

A protocol has been published.[16] Links to the manual of procedures and statistical analysis plan are provided in the manuscript. Community-level data are available in the appendix. Anonymised individual participant data and a data dictionary are available after approval of a proposal, available at https://osf.io/j5yqn/.

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