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Mass Chemoprophylaxis for Control of Outbreaks of Meningococcal Disease

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Summary

Although vaccination is the primary strategy used to control meningococcal disease outbreaks, mass chemoprophylaxis has also been used for immediate outbreak response either to supplement vaccination or when vaccination is not possible. However, public health guidelines from various countries vary regarding the use of mass chemoprophylaxis for outbreak control, in part because the impact of mass chemoprophylaxis on the course of an individual outbreak is difficult to assess. In this review, we review data from the use of mass chemoprophylaxis in the military and during 33 outbreaks of meningococcal disease. In a majority of outbreaks, either no additional cases occurred after mass chemoprophylaxis or cases occurred only in individuals who had not received prophylaxis. When cases did occur among prophylaxis recipients, there was often a delay of several weeks before these additional cases occurred. These outbreak reports suggest that mass chemoprophylaxis may provide temporary protection to chemoprophylaxis recipients during outbreaks.

Introduction

Meningococcal disease outbreaks occur when there are multiple cases caused by the same meningococcal strain in a community or institution over a short period of time and the cases are not linked by direct close contact. Depending on the size of the institution and specific circumstances, having just two cases of the same strain may be considered an outbreak,

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Contributors

All authors contributed to the conception and design of the review. LAM, JRM, and DSS participated in identification of papers for inclusion. LAM conducted the analyses and drafted the article; all authors revised the work critically for important intellectual content. All authors approved the final version and have agreed to be held accountable for all aspects of the accuracy and integrity of the work.

Conflicts of interest

We declare that we have no conflicts of interest.

while in other circumstances (particularly in community settings), two cases may instead be considered a cluster.^{1,2} While outbreaks account for only 2–3% of meningococcal disease cases in the United States each year (CDC unpublished data), each outbreak requires an immediate public health response to help prevent additional cases. Vaccination of the population at increased risk against the serogroup responsible for the outbreak is usually the recommended response for a meningococcal disease outbreak and is the best method to provide individuals with protection for the duration of the outbreak.¹ In addition to polysaccharide-protein conjugate vaccines against serogroups A/C/W/Y, the recent US licensure of two serogroup B vaccines means that meningococcal vaccines are now available to protect against the three most common disease-causing serogroups in the United States – B, C, and Y – as well as serogroups A and W. However, the serogroup B vaccines require multiple doses to achieve maximum protection and do not protect against all serogroup B strains.^{3–5} Furthermore, immunity following vaccination may take up to 2 weeks to develop, leaving even vaccinated persons susceptible to meningococcal disease during this period. For these reasons, mass antibiotic chemoprophylaxis for the population at risk has been proposed as an additional measure for outbreak control, either to supplement a vaccination campaign or as an independent measure when vaccination is not appropriate (e.g., no vaccine is expected to help protect against the meningococcal outbreak strain or no vaccine is licensed or recommended in the affected age group.)

Antibiotic chemoprophylaxis is routinely recommended for close contacts of meningococcal disease patients, who are estimated to have an up to 1600-fold increased risk of meningococcal disease compared to the general population.^{6,7} The goal of this chemoprophylaxis for intimate contacts is to eliminate colonization with *Neisseria meningitidis* before the bacterium causes invasive disease or is transmitted to others. In contrast, mass chemoprophylaxis can be broadly defined as the expansion of chemoprophylaxis beyond close contacts of cases in an attempt to interrupt meningococcal transmission on a broader scale. A key characteristic of meningococcal disease outbreaks is that outbreak cases are not all directly linked by close contact. Instead, an outbreak occurs when there is continuing transmission and acquisition throughout a population via asymptomatic carriage of virulent *N. meningitidis*. By reducing asymptomatic carriage in the population, administration of mass antibiotic chemoprophylaxis to the population at risk during an outbreak could in theory reduce transmission of the outbreak strain and prevent additional cases of disease. However, mass chemoprophylaxis is logistically challenging and could also have negative consequences, including the development of antibiotic-resistance and occurrence of adverse drug reactions in people receiving chemoprophylaxis. Public health guidelines from various countries differ as to whether mass chemoprophylaxis is recommended for outbreak control (Table 1).

The existing data on the effectiveness of mass chemoprophylaxis as an outbreak response have not previously been compiled in a single reference. To provide a resource for future decisions around mass chemoprophylaxis, this article summarizes past experience using mass chemoprophylaxis as a response to meningococcal disease outbreaks.

Agents for Mass Chemoprophylaxis

Currently, rifampicin, ceftriaxone, and ciprofloxacin are the primary antibiotics recommended for chemoprophylaxis of meningococcal disease among close contacts of meningococcal disease patients in the United States. These antibiotics would be the most likely choices for a mass chemoprophylaxis campaign. However, several other antibiotics have also been used for mass chemoprophylaxis in response to meningococcal disease outbreaks (Table 2). Table 2 summarizes the historical time period when agents have been used for meningococcal chemoprophylaxis and, when relevant, the reasons for discontinuation.

Sulfadiazine Chemoprophylaxis and the Development of Resistance

Mass chemoprophylaxis for meningococcal disease was first used in the 1940s in populations of US military recruits, which frequently experienced a high incidence of meningococcal disease.¹⁴ After an initial report demonstrated that mass administration of sulfadiazine was highly effective both in reducing meningococcal carriage and in preventing cases of meningococcal disease,¹⁴ sulfadiazine was used routinely for mass chemoprophylaxis in military populations for the next 20 years.²² In 1963, however, mass prophylaxis with sulfadiazine failed to stop an outbreak on a Naval base in California and testing of patients' meningococcal isolates revealed sulfadiazine resistance.²³ Additional reports of sulfadiazine resistance quickly followed,^{24,25} and the routine use of sulfadiazine for chemoprophylaxis was discontinued as resistance became widespread. Sulfadiazine resistance remains pervasive (~50%) among meningococcal isolates worldwide.²⁶⁻³¹ Meanwhile, vaccination of military recruits with meningococcal polysaccharide vaccines became commonplace beginning in 1971.³²

The experience with sulfadiazine in military populations demonstrated that mass chemoprophylaxis could be an effective measure to reduce the incidence of meningococcal disease, at least in closed populations where drug administration could be carefully monitored and controlled. However, the development and spread of sulfadiazine resistance shows that frequent mass antibiotic administration should be undertaken with caution and combined with ongoing surveillance of meningococcal isolates to detect antibiotic resistance.

Rifampicin and Minocycline Chemoprophylaxis in Military Recruits

Once sulfadiazine prophylaxis became ineffective, different antibiotics were introduced for mass chemoprophylaxis of meningococcal disease in military populations. Reports have been published describing three outbreaks in military populations where rifampicin³³⁻³⁵ or minocycline³⁶ was used for mass chemoprophylaxis (Table S1). One study in which ciprofloxacin was used in response to a meningococcal disease outbreak was excluded from this review, as insufficient detail was provided to determine how many cases occurred before and after the intervention.³⁷

In the two outbreaks in which rifampicin was used, the incidence of meningococcal disease was reported to decrease following mass chemoprophylaxis.³³⁻³⁵ In one instance no

additional cases were reported following chemoprophylaxis of meningococcal carriers (37% of base population) and vaccination of all personnel^{34,35} while in the other, case incidence after chemoprophylaxis (vaccination not mentioned) decreased to the level observed in a control population that had not been experiencing an outbreak.³³ However, development of rifampicin resistance among meningococci carried in the nasopharynx was observed in both instances. Meanwhile, in the outbreak in which minocycline was used, eight additional cases occurred beginning four weeks after administration of mass chemoprophylaxis (Table S1).³⁶ This population was, however, experiencing rapid turnover as new recruits entered the base, and by the time additional cases occurred, 61% of recruits in the base had arrived after the mass chemoprophylaxis regimen was administered (Table S1). Although serogroup C polysaccharide vaccine and an additional round of chemoprophylaxis were provided to all new recruits after the 13th case occurred, two additional cases then occurred in recruits not targeted for this second intervention. The study thus suggests that mass chemoprophylaxis may be less effective when it is administered to only a segment of the population affected by an outbreak. While one of the outbreaks ceased following chemoprophylaxis of only 37% of the population, meningococcal carriage in the population remained high and so vaccination and an additional round of prophylaxis were offered to base residents.^{34,35} Thus, the relative contribution of the initial round of chemoprophylaxis to control of the outbreak was not clear.

Community and Organizational Outbreaks

In contrast to military populations, outbreak responses in non-military organizations or in the community are more likely to face challenges achieving rapid and complete administration of antibiotics or vaccines. Thus, the data from community and organizational outbreaks exhibit substantial variability in how mass chemoprophylaxis was implemented and the population coverage that was achieved.

Rifampicin Chemoprophylaxis

Nineteen reports of rifampicin mass chemoprophylaxis during a meningococcal disease outbreak or cluster in non-military organizations or in the community were identified. Of these, one report was excluded because it was uncertain whether the situation described was truly an outbreak (3 cases in a community of 775 people over a 4 year period);³⁸ and one report was excluded because insufficient detail was provided to assess whether case incidence changed after chemoprophylaxis.³⁹

Of the remaining seventeen outbreaks, fourteen were organization-based and three occurred in communities. Four of the organization-based outbreaks occurred at nurseries or pre-school centers; one at a pre-school and associated school; one at an elementary school; one at an elementary and secondary school; six at middle and/or secondary schools; and one in a pair of hotels. The features of each outbreak and intervention, including cases occurring before and after mass chemoprophylaxis, are summarized in Table S1.

In 12 of these outbreaks, no additional cases occurred after rifampicin chemoprophylaxis.^{40–46} In four instances, vaccination was also provided to the target population around the time of chemoprophylaxis administration.^{41,43}

In one additional instance, a community outbreak with 12 total cases, serogroup A/C polysaccharide vaccination was provided to children aged 1–15 years after the first 4 cases but failed to stop the outbreak.⁴⁴ Five of the remaining outbreaks were due to serogroup B and therefore vaccination was not available;^{40–42, 45, 46} for the remaining two serogroup C outbreaks, information on vaccination was not reported.⁴¹

In the five outbreaks where additional cases did occur, antibiotic prophylaxis coverage was low (<70%) in two instances,^{47,48} while a third did not specify the antibiotic coverage achieved.⁴⁹ In one of these outbreaks, vaccination was administered only after additional cases had occurred;⁴⁷ the other outbreaks were caused by meningococcal serogroup B for which no vaccine was available. In the fourth and fifth outbreaks, additional cases occurred soon after mass chemoprophylaxis (and in one instance, vaccination) was administered but the cases occurred in persons outside the targeted population.^{50,51}

Although these reports suggest that mass chemoprophylaxis with rifampicin may provide protection to prophylaxis recipients during a meningococcal outbreak, especially if high antibiotic prophylaxis coverage is achieved, some of the outbreak responses included vaccination as an additional intervention. In these instances it is difficult to determine the relative contributions of vaccination and chemoprophylaxis in preventing additional cases. It is also unknown when these outbreaks would have ended without an intervention. Furthermore, rifampicin resistance was detected in all three reports that assessed the development of resistance among meningococcal carriage isolates after rifampicin administration.^{42,44,47} Thus, although these reports provide evidence that high coverage with rifampicin mass chemoprophylaxis may help prevent additional cases of meningococcal disease among prophylaxis recipients, they reinforce the concern that rifampicin resistance is likely to develop rapidly among carried meningococci.

Ciprofloxacin Chemoprophylaxis

We identified reports from nine outbreaks in which ciprofloxacin was the primary antibiotic used for mass chemoprophylaxis (Table S1). Six of these outbreaks occurred in organizations, including one in a nursery, one in a high school, one in a nursing home, and three in universities; one outbreak occurred within a single extended family; and two additional outbreaks occurred in community settings (Table S1). We also identified reports from one community outbreak in which ciprofloxacin and rifampicin were both used for mass chemoprophylaxis in an outbreak (Table S1).^{52,53}

Like rifampicin, mass chemoprophylaxis with ciprofloxacin appears to provide some protection to chemoprophylaxis recipients during a meningococcal disease outbreak. No additional cases occurred after chemoprophylaxis in four of the ten outbreaks or clusters reviewed.^{54–57} Concurrent use of vaccine was reported in only one of these outbreaks.⁵⁷ However, in six outbreaks or clusters, one or more additional cases did occur after ciprofloxacin chemoprophylaxis (Table S1). Vaccination was administered along with prophylaxis in four of these outbreaks (Table S1).^{52, 53, 58–60} In two outbreaks, the additional cases occurred in persons not included in the population originally targeted for chemoprophylaxis or vaccination.^{58,60} This reinforces the trend noted in previous sections and suggests that mass chemoprophylaxis is less likely to prevent cases if the entire

population at risk is not recognized and included in the intervention. In a third outbreak,⁴⁸ the additional case after prophylaxis occurred in the sole person in the target population who did not receive chemoprophylaxis. In a fourth outbreak,⁶¹ the first post-chemoprophylaxis case occurred days after the intervention in a person who had not received prophylaxis; additional cases in the population did not occur until 7 months later. In the fifth outbreak,⁵⁹ one case occurred one day after chemoprophylaxis and vaccination were administered, but whether the case was in an antibiotic recipient was not clear. Finally, in the sixth outbreak,⁵³ a case occurred one month after prophylaxis in a person who had received both ciprofloxacin and vaccine but who had a suboptimal response to the polysaccharide vaccine. Collectively, the reports suggest that mass ciprofloxacin chemoprophylaxis may provide at least temporary protection to those persons who receive the recommended antibiotic regimen.

The impact of ciprofloxacin mass prophylaxis on meningococcal carriage was assessed in only two reports.^{61,62} Both reports suggested that the mass chemoprophylaxis program reduced meningococcal carriage, but only one report assessed development of ciprofloxacin resistance.⁶² While no resistance was detected in this report, carriage was not assessed until 6 months after the intervention had taken place.

Other Agents

The use of intramuscular ceftriaxone chemoprophylaxis is described in response to a serogroup C sequence type (ST)-11 meningococcal disease outbreak at a primary and secondary school complex of 1,850 students in rural Oklahoma, 2010 (Table S1).⁶³ In this outbreak, chemoprophylaxis was offered to the population following one probable and four confirmed cases of meningococcal disease and vaccination was offered one week later. No additional cases occurred after the interventions.

We also identified one report of ofloxacin chemoprophylaxis in response to an ST-32 outbreak of serogroup B meningococcal disease at a college in Norway in 1992 (Table S1).¹⁹ Following three cases, ofloxacin was provided only to those carrying *N. meningitidis* (21.4% of the population). Vaccination was not attempted as no serogroup B vaccine was available. No additional cases occurred.

Azithromycin has been occasionally used for meningococcal chemoprophylaxis²⁰ and has been recommended for prophylaxis in the United States in areas where ciprofloxacin resistance has been identified among meningococcal isolates.¹ In one report, azithromycin was used as a chemoprophylactic agent (along with ciprofloxacin) in an outbreak setting after administration of rifampicin failed to halt the outbreak (Table S1).⁴⁹

However, two additional cases occurred in the population after azithromycin administration. We did not identify any reports in which azithromycin was used as the primary antibiotic for a mass chemoprophylaxis regimen in response to an outbreak.

Finally, we identified one report in which both sulfadimidine and penicillin were used for mass prophylaxis.⁶⁴

This report was the only one identified in which mass chemoprophylaxis was attempted in the meningitis belt of Africa, which experiences annual meningococcal disease epidemics during the dry season of each year (approximately December–June).⁶⁵ In this report, chemoprophylaxis was provided to four villages in Sudan in late March of the 1952 epidemic season, following 293 meningitis cases in these four villages since late January of that year. Two villages received sulfadimidine and two received penicillin; coverage ranged from 33–93% of each village and was 51% overall. While case incidence decreased after prophylaxis and was lower among prophylaxis recipients than among non-recipients, an additional 115 cases occurred in the villages by early May. Of note, case incidence in the African meningitis belt typically declines as the dry season wanes in April–May even in the absence of an intervention.

Discussion

In a majority of the outbreaks reviewed (19/33), no meningococcal disease cases occurred after mass chemoprophylaxis was implemented.^{19, 34–35, 40, 41–46, 54–57, 63} While additional cases occurred in the remaining outbreaks, these cases often occurred only in individuals who had not received the initial round of chemoprophylaxis, either due to refusal or because they were outside the targeted population.^{48, 50, 51, 58, 60} When cases did occur among prophylaxis recipients, there was often a delay of several weeks before these cases occurred.^{36, 48, 61} In only three outbreaks did additional cases occur in prophylaxis recipients within one month of prophylaxis administration.^{49, 52, 53, 64} Overall, the reports from these outbreaks indicate that mass chemoprophylaxis may provide temporary protection to prophylaxis recipients during an outbreak; however, targeting prophylaxis to the appropriate population is critical.

The impact of mass chemoprophylaxis on the course of a meningococcal disease outbreak or cluster is difficult to fully assess since we do not know what would have happened in the absence of the intervention. Meningococcal disease outbreaks eventually end even without public health intervention and we cannot tell how many cases, if any, were prevented by mass chemoprophylaxis in the reports reviewed. Furthermore, in at least 11 serogroup C outbreaks and one serogroup B outbreak, vaccination (with various meningococcal vaccines) was used simultaneously or shortly after mass chemoprophylaxis; and in several cases multiple rounds of chemoprophylaxis were used as well (Table S1). These factors further obfuscate the impact of mass chemoprophylaxis on the course of the outbreaks. However, when we include only serogroup B outbreaks that occurred prior to serogroup B meningococcal vaccine availability to remove the potential confounding effects of vaccination, a similar pattern emerges. Of these 13 serogroup B outbreaks, eight had no cases after chemoprophylaxis.^{18, 40–42, 45, 46, 54, 55} In two additional outbreaks, cases after prophylaxis occurred only in persons who had not received chemoprophylaxis.^{48, 51} Additional cases occurred in prophylaxis recipients within one month of chemoprophylaxis administration in only a single outbreak.⁴⁹

Six reports also provided sufficient information to assess the impact of mass chemoprophylaxis on overall meningococcal carriage. When carriage before mass chemoprophylaxis was compared to carriage after the intervention, a reduction of at least

70% was observed in all four reports where greater than 90% antibiotic coverage was achieved (Figure 1). In three of four reports rifampicin was used,^{33, 41, 51} ciprofloxacin was used in the fourth.⁶¹ This reduction in carriage was seen even when carriage was not reassessed until 6 weeks after prophylaxis; and in an additional report where carriage was not reassessed until 7 months after chemoprophylaxis, meningococcal carriage was still >50% lower than it had been prior to the intervention.⁴⁴

The only exception was one outbreak in which carriage was not reduced two months after mass chemoprophylaxis.⁴⁷ However, in this instance antibiotic coverage of the targeted population was only 65.5% and carriage was not assessed at an earlier time point after chemoprophylaxis to assess whether there may have been a transient impact on carriage prevalence.

The impact of mass chemoprophylaxis on carriage of the specific outbreak strains was difficult to assess. Limited sampling and the often very low carriage prevalence of the outbreak strain complicate interpretation of the data, but reductions in carriage of outbreak strains correlated with reductions in overall meningococcal carriage. Overall, mass chemoprophylaxis was associated with substantial reduction in meningococcal carriage and carriage of the outbreak-associated strains in the targeted populations, and the reduction in carriage usually lasted weeks to months after the intervention. These findings are consistent with a recent systematic review demonstrating that ciprofloxacin, rifampicin, and minocycline all reduce carriage of meningococci in controlled trials.¹⁶

Overall, the reports from these outbreaks suggest that, while mass chemoprophylaxis alone may not always halt an outbreak, it may provide at least temporary protection to prophylaxis recipients. However, it should be noted that publication bias may have led to a failure to publish reports from additional outbreaks in which mass chemoprophylaxis was not effective. We may also have failed to include relevant studies due to the language restrictions in our search strategy, or may have failed to identify pertinent articles through our search; however, omissions even of several relevant reports would be unlikely to change our primary findings. Finally, it should be noted that we identified only a single report of mass chemoprophylaxis use in the meningitis belt of Africa, the region with the highest incidence of meningococcal disease worldwide. Additional data on the potential impact of mass chemoprophylaxis in this region are needed.

Each of the outbreaks discussed in this article described a unique outbreak situation and response. Thus, features of outbreaks in which mass chemoprophylaxis is more likely to be successful were difficult to identify. Outbreaks in which no additional cases occurred after mass chemoprophylaxis included both serogroup C and serogroup B outbreaks, as well as community and organizational outbreaks; had target populations of widely varying sizes; and achieved varying degrees of antibiotic coverage (Table S1). Additional cases did occur in four of six outbreaks where only a part of a larger organization or community was targeted for prophylaxis (e.g. one residence hall at a larger university). This trend suggests that an important factor in the use of mass chemoprophylaxis is successfully identifying the appropriate target population. Defining the target population for vaccination is challenging, and may be more challenging for chemoprophylaxis due to the drawbacks of unnecessary

antibiotic use. Meningococcal disease outbreaks are often identified after only 2–3 cases have occurred; thus, limited information is available on the population at risk. The target population must therefore include not just the smallest population that contains the cases, but also the immediate social network of those cases that provides opportunities for meningococcal transmission.¹¹ The advantages of expanding the target group must be balanced against the challenges of providing the intervention to a larger group of individuals. This includes the additional cost, more complex logistics, and the potential for adverse reactions (Box 1).

In two of the outbreaks reviewed, individuals were tested for meningococcal carriage and chemoprophylaxis was administered only to those individuals who had meningococcal carriage identified.^{19,34,35} Although no additional cases occurred after chemoprophylaxis in either of these outbreaks, in one instance meningococcal carriage in the population remained high after chemoprophylaxis and so vaccination and an additional round of prophylaxis were offered to the full population.³⁴ Testing for meningococcal carriage takes several days, which means that by the time test results are obtained, carriers may have already transmitted the bacteria to others in the population. Furthermore, additional cases may occur while meningococcal carriage is being assessed. For these reasons, if mass chemoprophylaxis is pursued, screening for meningococcal carriage before administration of antibiotics is not advised.

In every report in which the time period of antibiotic administration was noted, antibiotics were dispensed to the target population over the course of a few days to a week at most. In a setting of continued transmission within the population at increased risk and an incubation period of one to 10 days between acquisition of *N. meningitidis* and disease, we would anticipate that transmission would be most effectively interrupted by administering antibiotics over the shortest time period possible. While attaining high coverage quickly is likely critical to the success of a mass chemoprophylaxis campaign, it is logistically challenging especially in larger organizations and community settings.

A key concern about the use of mass chemoprophylaxis is the potential development of antibiotic resistance. In the reports summarized above, rifampicin resistance was observed in meningococcal carriage isolates obtained from members of the targeted population after mass chemoprophylaxis in every instance in which rifampicin resistance was assessed. Nevertheless, resistance to rifampicin remains very uncommon among US meningococcal disease isolates.⁶⁷ Rifampicin mutations can result in a fitness cost for the organism's survival or invasiveness⁶⁸ and this may help explain the failure of many rifampicin resistance mutations to persist among clinical isolates.

The development of ciprofloxacin resistance after mass chemoprophylaxis in an outbreak setting was assessed in only one report;⁶² however, other studies of the impact of this antibiotic on meningococcal carriage did not detect the development of resistance immediately after ciprofloxacin use.¹⁶ Despite extensive fluoroquinolone use in the United States in the last two decades, < 1% of US surveillance isolates from invasive meningococcal disease cases are ciprofloxacin-resistant.⁶⁷ However, resistance or reduced susceptibility to ciprofloxacin has been identified in meningococcal isolates from around the

world (e.g. United States,^{67–69} Australia,⁷⁰ Europe,^{71–73} India,⁷⁴ China,⁷⁵ Singapore,⁷⁶ South Africa⁷⁷). A recent study of meningococcal isolates from Shanghai, China from 2005–2013 found 81% were resistant to ciprofloxacin and one additional isolate (3%) had intermediate resistance to ciprofloxacin.⁷⁵ These findings raise the concern that mass chemoprophylaxis with ciprofloxacin could contribute to the spread of ciprofloxacin resistance. Future studies are needed to better assess the impact of single dose chemoprophylaxis in the development of ciprofloxacin resistance in *N. meningitidis*.

Another concern is the potential for adverse effects of the antibiotics given in a mass chemoprophylaxis program. While most of the reports reviewed here identified no adverse reactions⁴⁴ or only self-limited reactions^{36,58} to the chemoprophylactic antibiotics used, serious adverse events can occur following administration of ciprofloxacin (e.g. anaphylaxis,⁵⁹ tendinitis and tendon rupture,^{78,79} see also Table 2) and other antibiotics. Therefore, it is important to educate recipients about potential adverse reactions and to actively monitor for these reactions. While meningococcal disease cases are devastating and can cause death or long-term sequelae, the potential for adverse reactions, emergence of antibiotic resistance, and logistical challenges must all be considered when deciding whether to pursue a mass chemoprophylaxis program in response to any particular outbreak.

Vaccination remains the best way to provide long-term protection to the population at risk during a meningococcal disease outbreak by providing direct protection to vaccinated individuals; in addition, several of the new A/C/W/Y protein-capsular polysaccharide conjugate meningococcal vaccines have been shown to impact meningococcal carriage over time.^{80,81} However, the new serogroup B recombinant protein vaccines directed at non-capsular antigens may not substantially impact meningococcal carriage.^{82–84} In either case, mass chemoprophylaxis can temporarily reduce meningococcal carriage in individuals before protection from a vaccination campaign can be achieved. Mass chemoprophylaxis could also play a role in reducing meningococcal carriage in organizational outbreaks where a vaccination campaign is not possible because no vaccine is expected to provide protection against the outbreak strain, vaccine is not available, or vaccine is not available for the affected age group. In this situation, it would be essential to ensure high antibiotic coverage, rapid administration, and accurate identification of the target population to maximize the chance of controlling transmission of the outbreak strain.

Overall, the outbreak reports reviewed here suggest that mass chemoprophylaxis may provide temporary protection to chemoprophylaxis recipients during outbreaks. As each meningococcal disease outbreak is unique, the balance of risks and benefits of using mass chemoprophylaxis will be different in each situation (Box 1). Unless the population is completely closed and carriage is eliminated in every individual, the population will remain at risk for reintroduction and spread of pathogenic meningococci, and occurrence of additional meningococcal disease cases. Therefore, mass chemoprophylaxis is most likely to be successful when the population at risk is clearly defined and logistics allow for immediate chemoprophylaxis of all targeted persons. Furthermore, if used, mass chemoprophylaxis should be administered simultaneously or closely in conjunction with the appropriate conjugate or protein-based meningococcal vaccine, when available, to provide longer-term protection of the target population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.**Considerations for use of mass chemoprophylaxis in response to an organizational outbreak of meningococcal disease**

- Size of target population
- Degree of mixing between target population and surrounding population
 - Ex: inmates of a prison have low mixing with surrounding population
 - Ex: residents of one dormitory on a college campus likely have high mixing with other students at the college
- Potential for prolonged transmission and exposure within the affected population
- Logistics of antibiotic administration, including:
 - Cost
 - Feasibility of obtaining high coverage to ensure all potential carriers receive antibiotics
 - Feasibility of administering antibiotics to full target population within a short time period
- Potential adverse reactions to the antibiotics
- Development of antibiotic resistance
- Availability of meningococcal vaccine that is
 - Expected to protect against the outbreak strain
 - Licensed for use in the affected population

Note: Mass chemoprophylaxis should never delay initiation of a vaccination campaign if vaccination is available and appropriate. In many situations, the drawbacks to mass chemoprophylaxis outweigh the potential benefits.

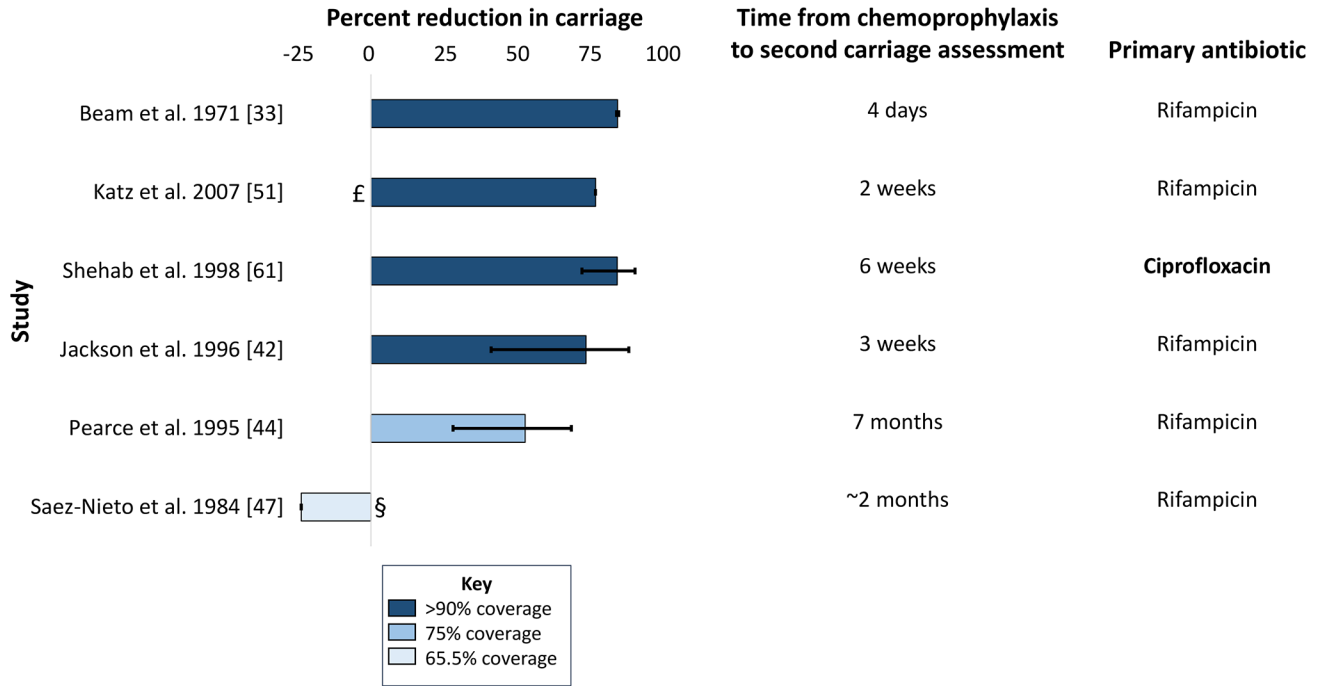


Figure 1. Reduction in *N. meningitidis* carriage after mass chemoprophylaxis during meningococcal disease outbreaks.

Data shown are the percent reduction in *N. meningitidis* carriage after use of mass chemoprophylaxis in response to meningococcal disease outbreaks. In five instances rifampicin was used; ciprofloxacin (bolded) was used in the remaining instance. Error bars are 95% confidence intervals (CI) for percent reduction in carriage in the target population calculated through the method of Zou and Donner.⁶⁶ When exact number of carriers was not reported, carriers were estimated from reported percent carriage. Only reports where an entire population (not just carriers) was targeted for chemoprophylaxis are included. See Table S1 for number of specimens tested and carriage prevalence at each time point. £Two rounds of chemoprophylaxis were conducted; carriage was assessed before the first and after the second. §95% CI not calculated as population tested for carriage was reported as larger than population targeted for chemoprophylaxis.

Guidance for use of mass chemoprophylaxis in response to outbreaks of meningococcal disease, selected countries

Table 1.

Country	Guidance for use of mass chemoprophylaxis in response to outbreaks
United States	<p>Guidance for all meningococcal disease outbreaks:¹</p> <ul style="list-style-type: none"> • Not generally recommended • May be considered for outbreaks involving limited, closed populations, especially for serogroup B (no serogroup B vaccines available at the time of writing) <p>Interim Guidance for Control of Serogroup B Outbreaks ^{*,2}:</p> <ul style="list-style-type: none"> • Not recommended as a standalone measure, but may be considered as an interim measure prior to achieving more long-term protection through vaccination
United Kingdom	<p>Health Protection Agency guidelines:⁸</p> <ul style="list-style-type: none"> • Recommended in pre-school groups • Recommended in schools and universities if a clear subgroup containing the cases can be defined • Can be discussed for community outbreaks and ones in schools and universities where a subgroup cannot be defined
Canada	<p>Public Health Agency of Canada guidelines:⁹</p> <ul style="list-style-type: none"> • Not recommended
Australia	<p>Communicable Diseases Network Australia guidelines:¹⁰</p> <ul style="list-style-type: none"> • Should be considered for organization outbreaks • Should not be used for community outbreaks

* Guidance written to address use of a serogroup B vaccine under an Investigational New Drug protocol, developed after use of this strategy in response to a high-profile meningococcal disease outbreak¹¹ and prior to licensure of serogroup B vaccines in the United States.

Table 2. Antibiotic agents that have been used for mass chemoprophylaxis of meningococcal disease

Agent	Currently recommended for close contacts in US? ¹²	Currently recommended for close contacts by European Centre for Disease Prevention and Control? ¹³	Time period in use for chemoprophylaxis	Reason for discontinued use	Resistance	Comments	Reference for impact on carriage
Sulfadiazine	No	No	~1943–63	Development of widespread resistance	Now widespread		14,15
Rifampicin	Yes, for all ages but not pregnant women	Yes, for all ages but not pregnant women	~1969–present	N/A	Frequently observed immediately after use ¹⁶ but not otherwise widespread	Rifampicin can interfere with efficacy of oral contraceptives and some anti-seizure and anticoagulant medications; may stain contact lens red. Not recommended in pregnancy.	16
Minocycline	No	No	1970s–80s	Frequent vestibular reactions (e.g. vertigo, nausea, vomiting) ^{17,18}	Has not been observed immediately after use ¹⁶		16
Penicillin	No	No	Not routinely used	N/A	No data found	While penicillin reduces meningococcal carriage compared with placebo, it is less effective than rifampicin, minocycline, or ciprofloxacin ¹⁶	16
Ofloxacin	No	No	Not routinely used	N/A	No data found		19
Azithromycin	No	Yes, all ages including pregnant women	Not routinely used	N/A	No data found	Can be used if ciprofloxacin resistance is detected	20
Ciprofloxacin	Yes, ages 1 month but not pregnant women [*]	Yes, all ages but not pregnant women [*]	~1980s–present	N/A	Has not been observed immediately after use ¹⁶	Historically, not usually recommended for persons <18 years due to concerns about cartilage damage (CDC 2013); however, review of data in humans did not identify irreversible cartilage toxicity in children or adolescents ²¹	16
Ceftriaxone	Yes, all ages including pregnant women	Yes, all ages including pregnant women	1980s–present	N/A	Has not been observed immediately after use; limited data available ¹⁶	Recommended for prophylaxis in pregnant women	16

^{*} Note that in the UK, ciprofloxacin is recommended for all age groups and for pregnant women⁸