A Critical Review of Control Strategies against Meningococcal Meningitis Epidemics in Sub-Saharan African Countries

J.-P. Chippaux, H. Debois, P. Saliou

Abstract

The control strategy of meningitis epidemics in sub-Saharan countries, although reexamined regularly, is based on epidemiological, immunological and logistical considerations put forward at the end of the 1970s. It comprises organizing large-scale vaccinations in the event of a declared epidemic. The obvious failure of this strategy recommended by the World Health Organization (WHO) necessitates evaluation of the emergency vaccination criteria. Despite current controversy on the immunogenicity of the polysaccharide vaccine, its safety, effectiveness in the field and low cost could justify the reopening of a debate on its use in routine vaccination. Routine – or preventive – vaccination could significantly reduce the incidence of meningococcal meningitis and its severity. The conjugate vaccine, when available, will constitute an additional advantage in the prevention of meningococcal meningitis. A strategy combining both polysaccharide and conjugate vaccines according to the population targets and possibilities for funding remain to be defined.

Key Words

Meningitis · Control · Immunization · Africa

Infection 2002; 30: 216–224
DOI 10.1007/s15010-002-3012-2

Introduction

In Sahelian Africa, where more than half the cases of *Neisseria meningitidis* meningitis reported throughout the world occur, meningitis epidemics account for one of the leading causes of death in people under 15 years of age, after diarrheic and respiratory diseases or malaria. The control strategy of meningitis epidemics is based upon the early detection of cases and the emergency vaccination of people living within the epidemic area [1, 2].

Three theoretical foundations underlie the choice of this strategy rather than preventive vaccination:

- the meningococcal polysaccharide vaccine (MPV) induces impaired immune response in infants under 2 years of age [3, 4], if not immunotolerance for polysaccharide C [5], while the single targets of preventive vaccination campaigns are often infants (Expanded Program on Immunization, EPI);
- polysaccharides fail to induce T-cell-dependent and thus long-lasting immunity [6], especially in infants [7–9];
- the incidence of meningococcus is low among young children within meningitis belt countries [4, 10, 11].

This strategy is currently much debated due to its obvious failure [12], as assessed by the high annual incidence of meningococcal meningitis in sub-Saharan countries (Table 1) and the possible effectiveness of preventive mass vaccination with cost recovery [13, 14].

In addition, serogroup C meningococcal conjugate vaccine (MCV) is already used as a preventive measure in some countries; a formulation under development that includes several serogroups is presented as the decisive alternative to allow preventive vaccination [6].

Strategy Options

The epidemiology of meningococcal meningitis in Africa was described by *Lapeyssonnie* in 1963 [11]. He specified the geographical perimeter of extension of epidemics and the climatic conditions contributing to their recurrence. He circumscribed the African meningitis belt between isohyetes 300 mm to the north and 1,100 mm to the south. Some 10 years later, the polysaccharide vaccine appeared to be a way of controlling these epidemics. Two conflicting strategies exist regarding the control of meningitis epidemics: emergency vaccination (also called appropriate vaccination or reactive vaccination) and preventive vaccination (also called prophylactic vaccination or routine vaccination). The choice of either of these strategies is based on epidemiological arguments (incidence, seasonal variation, recurrence and spread of epidemics), immunological

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Received: January 16, 2002 • Revision accepted: April 23, 2002

arguments (vaccine properties and immunogenicity, herd immunity, duration of protection), bacteriological arguments (emergence of new serogroups, carriage and transmission of bacteria) and operational arguments (cost and feasibility of vaccination campaigns, fund-raising, acceptance of interventions among the population). Each strategy can be adapted in its application (complete vs selective vaccination, narrowing vs broadening of the target population, free campaigns vs cost recovery, etc.).

During the 1980s, large-scale vaccination campaigns to prevent further epidemic outbreaks were implemented in many countries, notably Niger [13] and Benin [14]. The absence of coordination and the poor organization of these campaigns soon revealed the limits of this strategy. For various reasons mentioned below, the concept of emergency vaccination replaced the concept of preventive vaccination. The purpose was to counter early epidemics to curb their spread: a mass vaccination campaign every 5 or 10 years would replace annual vaccinations, thus resulting in significant savings for similar effectiveness, provided the epidemic is managed very early. Two requirements were immediately emphasized. The monitoring system for the collection of cases had to be effective and a compromise had to be reached between the specificity and the sensitivity of the alert threshold. Indeed, undue alerts due to excessive sensitivity or late response due to excessive specificity had to be avoided. The alert threshold was based on the analysis of an outbreak in Burkina Faso [15], then revisited after the epidemics occurred in the 1990s [16–18]. In the same way, the poor efficiency of this approach persuaded its promoters of the need for improved organization of vaccination campaigns. The implementation of security stocks and epidemic management committees as well as the creation of the international coordination group in charge of vaccine need assessment and the coordination of their distribution failed to bring significant changes to the current situation.

Figure 1. African meningitis belt [11].

Table 1
Number of cases reported to WHO from countries of the African meningitis belt.

	1995	1996	1997	1998	1999	2000	2001
Benin	165	699	360	1,115	346	1,326	7,532
Burkina Faso	1,320	42,129	21,504	5,629	3,215	3,178	10,897
Cameroon	?	178	?	2,887	2,272	1,492	?
Central Africa	?	155	10	245	757	3,069	1,816
Chad	30	1,079	158	7,961	2,540	7,729	5,780
Ivory Coast	?	?	?	3	94	22	?
Ethiopia	247	771	?	?	175	855	6,266
Eritrea	?	?	7	1	3	?	?
Gambia	?	?	913	?	?	252	137
Ghana	26	479	18,551	1,049	527	669	?
Guinea	238	89	51	58	507	325	?
Guinea Bissau	?	?	?	112	2,836	?	?
Liberia	?	?	?	101	114	?	?
Mali	1,199	7,254	10,960	2,704	1,038	816	?
Mauritania	?	0	11	18	259	251	?
Niger	26,738	16,145	3,922	2,328	5,510	13,873	4,014
Nigeria	100	77,089	?	5,948	1,946	711	?
Senegal	?	?	13	977	4,939	?	415
Togo	?	517	2,845	335	249	229	?

?: information not available

Epidemiology

The observations and conclusions of *Lapeyssonnie* have been widely accepted. The season cycle and the recurrence of epidemics have been confirmed and are still clearly marked. Epidemic areas correspond to the African Sahel, within what *Lapeyssonnie* called the "meningitis belt" (Figure 1). A few epidemiological characteristics likely to have changed over the past 40 years or so should, however, be emphasized.

High-Risk Population

Some epidemiological studies have shown that the incidence of meningococcal meningitis is lower in infants aged under 2 years [4, 10, 11]. In Niamey [19, 20], the specific incidence of meningococcus is similar in infants aged below 1 year (37.4 cases per 100,000 infants outside epidemic periods and 496 cases per 100,000 during epidemic periods) to that in the 1–20-year age-group (36 cases per 100,000 subjects outside epidemic periods and 490 cases per 100,000 during epidemics). Indeed, below the age of 1 year cases of *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* bacterial meningitis remain the most frequent and the most deadly [19].

The change in the distribution of meningitis cases according to age, observed in temperate countries during epidemic periods [21], has not been confirmed in meningitis belt countries [20] where this factor is unable to serve as an alert indicator.

Increase in the Number of Cases

Both rural and urban areas might be affected. Various factors have been incriminated. Higher promiscuity that might result from the economic crisis, especially in cities, was emphasized [22]. Paradoxically, vaccination coverage was held responsible for a lower natural immunity of the population, since MPV does not induce immune memory [23]. This argument has been contradicted by facts. It is unanimously acknowledged that vaccination coverage is very low and probably insufficient to interfere with natural immunity, at least in meningitis belt countries. Furthermore, the incidence of meningitis in adults has not changed over the past 30 years, which tends to show that their immunity has been maintained.

High urbanization in Africa has been accompanied by urban epidemics with strong media impact. Seasonal migrations, especially during the dry season when agricultural activity is suspended and when the population looks for urban activities, increase the risk of urban epidemics. Impoverishment – and consequently higher promiscuity, poorer hygiene conditions and lower health care supply – may account for an increase in incidence. However, due to the general increase in the population, raw incidence has not increased significantly and the higher number of cases is more probably a measuring artifact (Figure 2). Besides, such an increase could reflect the improvement in the monitoring system observed in most countries.

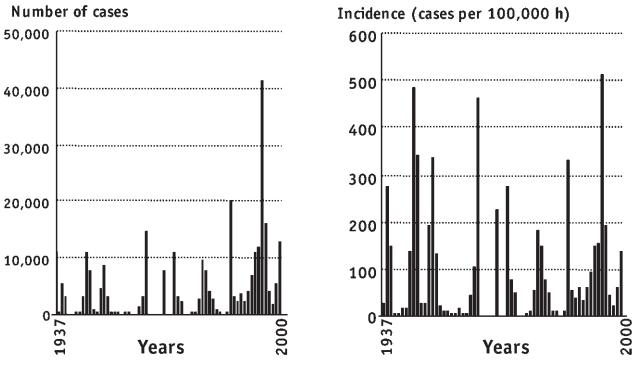

Figure 2. Incidence of meningitis in Niger between 1937 and 2000 (source OCCGE and OMS).

Extension of the Meningitis Belt

Since 1985 many epidemic outbreaks have occurred outside the usual limits of the meningitis belt [2, 24]. This extension is apparent both in the surroundings of the gradually growing meningitis belt, where outbreaks occurred in areas barely affected before [25] and remotely, in countries distant from the meningitis belt, such as Rwanda or Tanzania, that had never experienced this type of epidemic before. Climatic changes, especially desertification, may account for the extension to the neighboring countries. Human migrations, especially during the dry season – the season of maximum transmission – may be responsible for the remote spreading of the bacterium. The pilgrimage to Mecca, for example, plays a significant role in the spreading of the epidemic throughout Africa [2]. Local economic and sanitary conditions may facilitate the dissemination of the meningococcus in countries outside the meningitis belt. Epidemic extension out of the meningitis belt borders may be linked to the desertification, leading to an actual extension of the belt. However, endemicity of meningitis in countries remote from the current limits of the belt remains an hypothesis which will only be confirmed if outbreaks become recurrent in these areas.

Clinical Aggravation

The high lethality associated with certain serogroups, serotypes or clones suggests that they result in a higher transmission and a more severe illness. For the time being, this phenomenon, mentioned during the *N. meningitidis* A:4:P1.9 clone III-1 pandemic [26], has no epidemiological confirmation because comparison between different epidemics are difficult: data are not precise nor reliable. The high lethality (50%) observed during the *N. meningitidis* W135 epidemic in Gambia affected only six patients [27] but it amounts to 32% in a series of 109 cases in Saudi Arabia [28]. In addition, high lethality is often observed in the early epidemic period, whatever the serogroup involved, before appropriate therapeutic dispositions have been taken.

Average lethality during most epidemics remains at 10%, even with appropriate antibiotic treatment [2].

Dissemination of the Bacterium

It is now acknowledged that *N. meningitidis* dissemination is imputable to healthy carriers rather than to sick people [2, 22]. This has two consequences. Firstly, the extension of the epidemic is anterior to the occurrence of the first cases since they reflect the increase in the carriage among the population. Secondly, the prophylactic measures taken for the sick people and their contacts are palliative measures that only have a limited impact on the course of the epidemic. The relevance of selective vaccination campaigns [4] targeted towards a limited population soon appeared insignificant, since the contaminating subjects were more scattered and collective immunity plays a key role in the control of the epidemic [29].

On the whole, it does not seem that these factors have significantly modified the epidemiological characteristics of meningitis epidemics in Africa since being described by *Lapeyssonnie* [11]. These characteristics cannot justify the exclusion of either of the two vaccination strategies.

Immunology

N. meningitidis induces a humoral immune response [30, 31] occurring 1 week after contact with the antigen (a bacterium in the case of an infection or a vaccine). Bactericidal antibodies are directed against capsule polysaccharides, outer membrane proteins and lipopolysaccharides. It is generally admitted that only bactericidal antibodies are correlated with the acquired level of immunological protection [30].

Maternal antibodies protect infants until about the age of 3 months. Immunization is then gradually acquired either following direct contact with the organism or by cross-immunization with saprophytic or slightly pathogenic bacteria akin to *N. meningitidis* [32]. The MPV is very well tolerated and its effectiveness in subjects over 4 years of age has not been challenged.

Debate mainly concerns the acquisition of immunity and the duration of protection conferred by the vaccine according to age. In this respect, opponents of preventive vaccination present MCV as a remedy for the weaknesses of MPV, which makes MCV the ideal candidate for routine vaccination.

Immunogenicity in Infants

The polysaccharide vaccine is reputed to be hardly immunogenic in children under 2 years of age. The two main capsule antigens, polysaccharides A (PSA) and C (PSC), induce distinct immunological responses. Most of the evaluations of MPV immunogenicity have been performed without bactericidal antibody titration, which limits their relevance [30]. A clinical trial on MCV during which the MPV was used as control showed that the latter induced a complex immune response [33]. With MPV, PSA causes bactericidal antibodies to appear and induces significant immunological memory, the effect of which is a very strong increase in bactericidal antibody titers after a booster injection simulating antigenic aggression. In contrast, PSC only results in a low immune response, even after a booster injection (Figure 3).

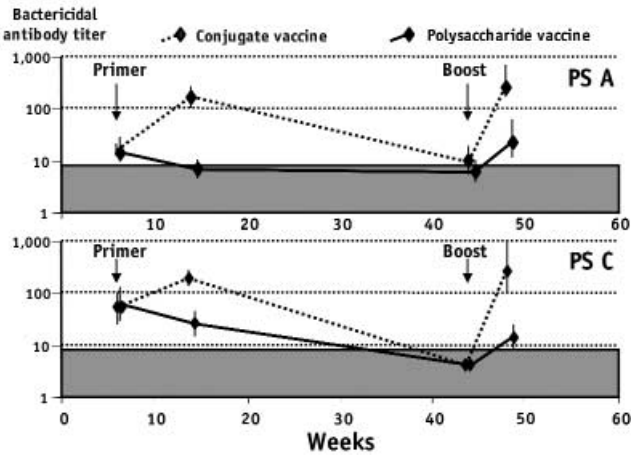

Figure 3. Compared immunogenicity of MPV and MCV in infants [33].

"Immunotolerance" towards Serogroup C

Early vaccination with PSC may induce a defective specific immunological response some authors have termed immunotolerance [5, 34]. The term is inappropriate since it would imply an absence of response or, at least, a response that would be lower than the protection threshold, which is not the case. In addition, this observation has not been confirmed by all the studies. This complex phenomenon requiring further investigation should prompt caution in the choice of a mass or routine vaccination strategy with PSC. This does not constitute an absolute contraindication to the vaccination of young children since bactericidal antibody titer increases significantly on further contact with the antigen and this titer is superior to the minimum level considered protective. In addition, serogroup A accounts for more than 85% of the isolates identified within the meningitis belt [20].

The response to PSC induced by MCV does not seem to be defective, even though it is less marked than with PSA. Consequently, MCV may be recommended in infants to prevent "immunotolerance" to serogroup C.

Effectiveness and Duration of Protection

Peltola et al. [35] observed an incidence rate of 40/100,000 cases of meningococcus A meningitis among non-vaccinated children, while no cases were reported in children between 3 months and 5 years vaccinated with PSA. *Reingold* et al. [9] showed that the effectiveness of a single vaccination gradually faded during the 4 years following its administra-

tion. However, protection lasts at least 1 year in all the children vaccinated before the age of 4, which protects them against the epidemic wave occurring the following year, a commonly observed phenomenon [36]. *Reingold* et al. [9] propose that MPV does not induce any immunological memory, without providing evidence for this hypothesis. In addition, they did not analyze the effect of a booster on vaccine effectiveness. Some authors who do not consider the use of several doses of MPV, recommend a vaccination schedule including three to four MCV injections for the routine immunization of children [37]. Indeed, the majority of studies showed that the duration of protection was not more than 3 or 4 years. Several have shown that effectiveness is maintained without notable reduction up to 3 years after vaccination, even in the absence of booster, in children [38] as well as in adults [39]. According to *Zangwill* et al. [40], the immune response lasts more than 10 years in adults. This leads us to conclude that the duration of protection of the MPV is probably clearly longer than the duration recommended by manufacturers. Repeated infections with *Neisseria* may even strengthen immunity and play the role of "natural boosters." Although it is still too soon to determine the duration of protection of MCV, we can expect it to be similar, if not superior, to the duration of protection of MPV.

Herd Immunity

Herd immunity, the mechanisms of which are still unclear, holds a key place in the control of epidemics. Its close link with the pharyngeal carriage of the meningococcus and the mucosal immunity, carried especially by IgA [41], led a few authors to measure the impact of the vaccine on carriage and on mucosal antibody production. The bacteriological studies on carriage are mentioned below. An increase – mostly transient – in specific salivary antibodies against PSA and PSC has been observed following vaccination with MPV [41, 42]. These two teams keep in mind that the Hib polysaccharide vaccine induces a mucosal immune response.

In addition, the decrease in the incidence of meningitis in nonvaccinated subjects after a vaccination campaign supports the hypothesis of an effective herd immunity [12, 43–45] even though the reasons for this remain largely unclear [46].

Bacteriology

Capsular polysaccharides and outer membrane proteins do not only play an immunological role. They are involved in virulence, especially the fixation of the bacterium to the pharyngeal epithelium, its resistance to phagocytosis and its permeation through the respiratory mucosal membrane. It is therefore essential that capsular polysaccharides and outer membrane proteins be identified during meningococcal infections. This also enables the dispersion of a strain to be followed and its circulation during the epidemic to be determined.

Rhinopharyngeal Carriage

The epidemiology of *N. meningitidis* carriage is not well known. We simply know that it changes with seasons, it is usually asymptomatic and it probably represents the main factor of dissemination of the bacterium and thus the first responsible for epidemics [22, 32, 47, 48]. The anteriority of carriage over the spreading of the epidemic and its asymptomatic nature significantly reduce the relevance of the control measures of the epidemic after it has started [2]. Only the immunity of contact subjects at the time when carriage appears can limit the dissemination of the epidemic.

MPV has no effect on previously established carriage [49]. It seems, however, that it significantly reduces contaminations occurring after its administration [50].

Whether MCV has the capacity to reduce carriage remains to be determined. Like the Hib conjugate vaccine [51], MCV is likely to have a significant impact on inter-human transmission. However, it is very important to assess whether routine utilization of MCV would induce mutations of the capsule antigens.

Emergence of New Serogroups

The emergence of new serogroups has also been emphasized to explain the aggravation of epidemics, regarding the incidence, hypothetical as indicated above, as well as the severity of the disease. Serogroup A remains the most frequent in sub-Saharan Africa. Monitoring carried out over 18 years confirmed that this serogroup accounts for more than 85% of the strains isolated in Niamey [19]. *N. meningitidis* C epidemics have also been reported in Nigeria (1975), Burkina Faso (1979), Mali (1979), Niger (1992) and during more or less important epidemics. Sporadic cases or localized epidemics of *N. meningitidis* X have been reported here and there, mostly during inter-epidemic periods [52]. More recently, a few *N. meningitidis* W135 strains were isolated during epidemics where serogroup A prevailed [27]. During spring 2001, a joint mission of the Pasteur Institute in Paris and the Association for Preventive Medicine isolated serogroup W135 in Burkina Faso and in Niger in proportions never reached before (37% and 40% of samples isolated during a short period at the end of the epidemic, respectively) [28, 53]. The reason for this emergence is unclear: a bias of sampling, a natural antigenic variation better identified thanks to well-mastered technology or the response of the bacterium to vaccine pressure. The latter argument has been used by supporters of emergency vaccination who believe that reducing vaccine pressure would prevent the emergence of antigenic variants.

Operational Constraints

Argumentation is complex and often speculative. No experimental data are available and discussion can only be based on the interpretation of observations. It turns out that studies aimed at comparing the different strategies or their modalities were rare; the conclusions drawn often lack objectivity and discrimination.

Thresholds and Alert

Besides the difficulty of reaching a compromise between specificity and sensitivity, political pressures underlie the debate. While, in a few countries, epidemiological monitoring proved satisfactory, most countries lack the means necessary to collect and/or forward the relevant information to the level of decision making. The declaration of epidemics is delayed by several weeks, thus resulting in the outbreak of hundreds of cases. Even when the criteria have been met, the decision to declare the epidemic remains the privilege of political authorities who can delay this declaration until a more favorable time.

It appears more and more that this waiting period is independent of the technical choices and accounts for the leading cause of failure of the emergency strategy.

Cost of the Vaccine

Depending on the studies, the cost of MPV administration is between 0.3 and 0.5 EUR [36, 54]. This cost includes the vaccine and its transport, cold-chain maintenance, disinfecting and injection equipment (auto-disable syringes) and the destruction of the material after use. The vaccine itself accounts for approximately half this cost. The price of the C monovalent MCV is between 11 and 22 EUR for national adjudication in single-dose presentations. As *Robbins* et al. [55] point out, the cost argument for ruling out MPV as part of a preventive strategy is reinforced for MCV. With MCV, the cost of logistics will only account for 10% of the cost of vaccination.

Operational Cost

The cost of an intervention, recurrent but discontinuous, and the cost of permanent action are often set against each other [56]. The cost of each of the two strategies has never really been calculated. We often simply compare special expenses, not planned in the national budget, to current running expenses scheduled each year. Two theoretical studies, based upon different models, have led to contradictory conclusions. The first study [57] based its model on the poor results of the vaccine in the long term, disastrous vaccination coverage and a high unit cost of the product, thus concluding in favor of emergency vaccination, with identical cost but much better short-term results and coverage. The second study [58] based its model on the results of the EPI, without considering that this program is implemented only for a small part of the population. In addition, all the costs, especially the loss of a significant number of doses, are not taken into account [59]. Several epidemics have been used as models to compare the effectiveness of each strategy or the number of cases avoided. The situation observed is usually opposed to a theoretical evolution based on a mathematical model. In this respect, the epidemic that affected Ghana is a perfect example. Indeed, the model indicated that preventive vaccination would have spared 61% of cases, thus coming to a result similar to properly conducted emergency vaccination if the alert had been given timely in compliance with WHO recommendations and if the epidemic had been declared immediately [60]. In practice, only 23% of cases were avoided during this epidemic despite very favorable conditions: increased monitoring due to declarations of epidemics in the neighboring countries and mobilization of vaccination teams thanks to a mass vaccination campaign against yellow fever carried out at the time when the epidemic broke out [61]. Surprisingly, despite such figures, authors still support emergency vaccination at the expense of routine vaccination. The controversy that followed shows the partial nature of the arguments aimed at replacing MPV by MCV [59, 61, 62) and the need for a more objective analysis of the operational causes of the repeated failures of emergency vaccination in order to encourage research on new strategies [63, 64].

Only one "experimental" study showed that not only preventive vaccination spared a larger number of subjects but also that its cost was less than half, amounting to savings of 0.3 EUR per inhabitant [65].

The cost of a mass vaccination campaign against an epidemic must take into account the number of vaccinations (theoretically for the whole population) and the expenses associated with emergency intervention: transport of vaccines and injection equipment, logistics, personnel, etc. The cost involved in antibiotic treatment of affected people and the burden of patients with sequels accounting for 15% of meningitis cases should also be taken into account [66]. The vast majority of resource comes from international and humanitarian aid mobilized in case of epidemics only.

Routine vaccination applies only to that part of the population not immunized during previous campaigns. After vaccination catch-up which applies to the whole population, this mainly represents each new generation, i.e. approximately 7% of the general population, taking into account boosters, to which we may add migrants in varying number depending on the communities. Catch-up can be implemented either following a mass campaign during an epidemic period or by population section during routine campaigns. In addition, the logistic cost is limited since routine vaccination is scheduled: the expenses associated with transport and personnel are lower, the price of the vaccine can be negotiated. Outside epidemic situations, it is ethically conceivable to share out the cost of vaccination and request community or individual contribution; contributions can also be requested from institutions (local authorities, decentralized cooperation, nongovernmental organizations or private sector). We may expect not only a significant reduction in the cost of patient treatment, but also savings due to prevention of serious neurological sequels.

Organizational Difficulties

One argument often put forward by routine vaccination detractors is the problem of implementation, as shown by the vaccination coverage obtained with the EPI [37].

While the EPI is by no means the perfect answer, it cannot be considered a complete failure. The incidence of a certain number of vaccine-preventable diseases has signifi-

cantly decreased since the EPI was widely implemented, especially in urban areas. It seems that partial vaccination coverage is enough to protect the community and that the repeated vaccination of individuals is superfluous and brings about sufficient herd immunity despite incomplete individual coverage.

Conversely, the organization of mass vaccination campaigns is not without problems limiting their impact, if not posing a threat to the population: vaccines containing too much solvent, if not fake vaccines, vaccine administration in appalling conditions resulting from logistic problems associated with panic, etc.

The main problem raised by emergency vaccination is vaccine supply. It is not possible for vaccine manufacturers to anticipate accurately the production of meningococcal vaccines and these vaccines are currently manufactured "just in time." On regular occasions, the world's stock in vaccines failed to meet the needs induced by widespread epidemics, especially when outbreaks occurred simultaneously in several countries [67]. Security stocks only provide a temporary answer until a more appropriate number of vaccines can be supplied. The virtual stock of the international coordination group is both insufficient to face several outbreak sites and too slow to implement. Scheduled routine vaccination would allow a better management of the production and control of vaccine stocks. In addition, in front of the mobilization of manufacturers over MCV vaccines, a mutual agreement between international authorities and manufacturers should rapidly come out in order to guarantee vaccine availability until an optimal strategy is defined.

Feasibility of Routine Vaccination

The feasibility of routine vaccination is controversial but it has never been studied. No original strategy has even been considered until now. The alternative between mass vaccination and EPI should be replaced by new strategies utilizing all the available resources: national immunization or health care days, institutions and associations, health or school systems, etc. We know that mothers are disposed to rally and take part in preventive vaccination campaigns and even contribute financially to cost recovery [14]. The fact remains that when the strategy is adopted, acceptable and relevant conditions of application will still have to be defined.

Conclusion

We are willing to convince defeatists who believe that MPV could only be used as a way to counterattack epidemics that preventive vaccination may well ensure their control. A low immunogenicity in infants and the operational difficulties of routine campaigns are usually the main arguments in favor of a restriction of MPV to emergency vaccination [2].

We have shown that the arguments put forward have to be reevaluated, taking into account the epidemiological and socioeconomic characteristics of meningitis belt countries. The protection of a majority of the population and probably a significant reduction in the risk of epidemics can be expected with MPV. Yet, this hypothesis deserves impartial and unbiased examination, which is not the case today.

MCV has definite advantages. Its excellent immunogenicity in infants is an appropriate answer to one of the main weaknesses of MPV. However, many factors remain undetermined such as the duration of protection and the impact on carriage, where advantages over MPV still have to be demonstrated. In addition, its cost which is *a priori* much higher than the cost of MPV, may well hinder its development in sub-Saharan Africa.

As is often the case, technological progress is presented as the solution to the setbacks met during the implementation of a method to control epidemics. We believe that the development of a new, better tolerated product that would be more effective or more easy to use is essential. It should not, however, represent a sort of blind pursuit and conceal the need for a better operational application of available tools in first intention, especially if they are well tolerated, effective, easy to use and not too expensive.

For this reason, we support the joint use of both vaccines which, too often, have been set against each other, resulting in the exclusion of one at the expense of the other. A preventive strategy could combine the routine administration of MCV in infants and a booster, or primary vaccination catch-up, with MPV in subjects aged over 2 years on an occasion to be determined (first admission to school, military service, occupational medicine, etc.). Operational research is required to determine more accurately the conditions of application of this strategy (vaccine association, age of primary vaccination and boosters, organization and target population of vaccination catch-up) as well as the necessary financial support (cost recovery, contributions from institutions, etc.).

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