Annex N

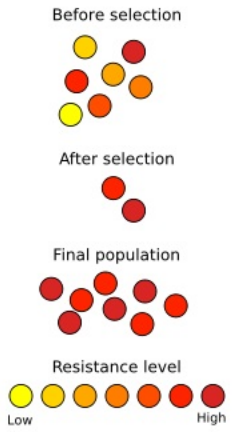
Monotherapy and the Evolution and Spread of Resistance

Monotherapy is defined as the provision of a single therapy to treat a single disease, whereas combination therapy is the use of more than one therapy to treat a single disease, usually in dosage forms containing more than one active ingredient (the pharmaceutical components that target particular molecular sites on the disease organism).

Combination therapy is now the global standard for the treatment of tuberculosis, cancer, leprosy and HIV/AIDS. To treat any of these diseases with monotherapy is now deemed unethical. The same argument can easily be made for its application to malarial disease.

Combination therapies are usually more expensive than monotherapies. However, the single unit costs of combination therapies do not take into consideration the indirect savings gained from deploying them.
Combination therapy results in lower treatment failure rates, lower case-fatality ratios and, most important in the context of malaria control today, slows the development and spread of drug resistance.

The reason combination therapy slows the development and spread of drug resistance, compared to monotherapy, can be explained in evolutionary terms. Drug resistance, whether against antimalarials, antiretrovirals or antibiotics, occurs through random genetic mutation (conferring some element of fitness in the disease organism), which is then selected for by non-random removal of less fit individuals that would otherwise contribute to the gene pool of the next generation (i.e. individuals that are biologically less fit are less likely to reach reproductive maturity and produce offspring). The simple graphic below illustrates this point (red dots represent organisms with a genetic mutation conferring some reproductive/survival benefit, whereas the yellow dots represent organisms without this mutation).



In effect, this natural selective process is a genetic filter, with the genes of fitter organisms becoming more numerous in the population over time. Random genetic mutation events that confer a selective benefit for malarial parasites against antimalarial drugs are actually quite rare. However, once they occur, the filtering process from one generation to the next can result in a relatively rapid increase in the ratio of resistant individuals versus susceptible individuals (as shown in the graphic above). While such mutations are rare, they do and have occurred. Almost every antimalarial monotherapy treatment deployed to date has become ineffective as a result of the emergence and subsequent spread of resistant parasites. Combination therapy aims to reduce this threat by exposing the disease organism to different chemical compounds that have different molecular target sites or modes of action. In effect, the rarity of beneficial mutation events is exploited, as the chances of a mutant emerging that is simultaneously resistant to two separate active ingredients with different modes of action is very small indeed; it is actually the product of respective mutation rates, multiplied by the number of parasite cells exposed to the drugs. This is a critically important point. During an acute malaria episode, a person will typically have between 10^9 and 10^{14} asexual parasites in their bloodstream. A mutational event that confers complete resistance to any single drug might occur at a frequency of $1{:}10^{10}$. Remembering that the chances of a simultaneous mutation occurring that confers resistance to two compounds with different modes of action is actually the product of respective mutation rates, multiplied by the number of parasite cells exposed to the drugs, we quickly see that the probability of such a mutation (resistant to two separate drugs) in this instance is $1{:}10^{20}$. A biomass of more than 10^{13} parasites in a single person is actually physically impossible. In summary, the deployment of combination therapies delays the development of resistance significantly. In the past whenever resistance to the most common antimalarial has emerged and spread, the global malaria control community has merely switched to a different treatment. However, currently there is no replacement for artemisinin and alternatives are not likely to be available for several years. As a result, delaying the development and spread of resistance to this class of compounds is a human rights imperative.[1]

[1] For a more detailed summary, see *Antimalarial drug resistance,* N.J.White, The Journal of Clinical Investigation, Volume 113 Number 8 April 2004