“Swantisept”
a new antbiotic for fighting infectious blindness Trachoma in Eritrea

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Rüdiger Schwan Ph.D. The University of Leeds, England, Great Britain
Home Adress: Fulda, Germany

Summary

Trachoma is the leading preventable cause of infectious blindness worldwide. Many people living in Eritrea are also affected by *Trachoma* besides other so called *Neglected Tropical Diseases* like *Leshmaniasis, Schistosomiasis, Leprosy, Dengue Fever* and soil transmitted *Helmenthiasis*, inspite of community based *Trachoma* prevalence in some endemic regions in the country, developed strategic plans of action like SAFE in collaboration with ITI, WHO, UNICEF and already initiated Mass Drug Administration (MDA).
Recent research on the essential microorganisms/bacteria (*Chlamydia trachomatis*, strains A, B, Ba, and C) in question, leads to hopes for novel therapy schemes and possibly also control of *Trachoma* by the year 2020.
“Swantisept”, a fairly new antibiotic, based on mainly natural sources, seems to be able to support already implemented control programs and tackle successfully or eventually eliminate *Trachoma* in Eritrea as a common development goal.
The range of application includes besides others like *Trichiasis*-surgery to halt corneal damage, environmental improvements, fly control and proximity to domestic animals and antibiotic treatment (single-dose *Azithromycine*):

--- oral therapy/dosage, (**“Swantisept-oral”**)
--- facial cleanliness/hygiene, water desinfectant
(**“Swantisept-safe”**)
--- topical treatment, eye-ointment (**“Swantisept-eye-drops”**),

the latter being discussed in more detail in this paper, because a small eye-drop unit is available already here in Asmara although with very limited production capacities at the moment to support immediately and efficiently the existing Blindness-Prevention and Control- Program based on the National Trachoma Prevalence Survey in collaboration with The Ministry of Health of the State of Eritrea, support from the Fred Hollows Foundation for instance and hopefully **“Swantisept”** in the near future.

Introduction

Some people say: “People who do not live in poverty do not get *Trachoma*”. However, not all populations living under poor conditions are afflicted by *Trachoma*, as poverty itself is not the direct cause of *Trachoma*. Rather, *Trachoma* thrives in areas where personal and community hygiene and priorities such as adequate food, shelter and warmth may take precedence. *Trachoma* is the leading cause of infectious blindness worldwide with nearly 1,8 million blind from *Trachoma* and 94 million with *Active Trachoma*. Afflicted people live in communities and their visual impairment may become an additional burden on their already strained family and community.

Trachoma progressively disappeared from the whole of Europe and North America and many other parts of the world over the past century, as living conditions improved. It has been more challenging to identify specific personal habits and particular conditions that expose an individual to increased risk of *Trachoma*, however much research has been carried out to this end.

We in Europe, especially Germany cannot, with good conscience, sit and wait for the gradual improvement in socio-economic status in developing countries like Eritrea to emulate gradual decline in *Trachoma* that occurred in developed countries. Thus, specific strategies having been started already need to be developed further to target those aspects of conditions identified as strong risk factors for *Trachoma*. In addition, effective treatment strategies and sophisticated antibiotics like **"Swantisept"** already exist for people afflicted with the disease, which can be implemented now.

Aetiology

Trachoma is a form of *Chlamydial kerato-conjunctivitis*. Members of the genus *Chlamydia* are obligate intracellular bacteria, which have all the elements of bacteria except a rigid cell wall. Of the three species causing disease in humans, *Chlamydia trachomatis* is the most common as a major cause of genital infection and conjunctivitis. A chronic form of *Chlamydia trachomatis conjunctivitis* is called *Trachoma*. Infection with the obligate intracellular Gram-negative *Chlamydia trachomatis* causes this self-limiting conjunctivitis, however, repeat infection causes active, infective or *Inflammatory Trachoma*.
Actice Trachoma is most prevalent in young children and the prevalence of disease decreases as children reach their later teenage years. Multiple episodes of *Active Trachoma*, particular intense disease, can lead to scarring of the tarsal conjunctiva. Scars are recognized as easily visible white bands, which are initially sparse but over time, they become more prevalent and form a thick basket-weave pattern. Significant scarring will contract the tarsal conjunctiva, causing the lid margin to roll toward the eye and bringing the lashes against the globe. The abrasion of the lashes on the cornea is painful and if left untreated, will rapidly produce scarring and opacification of the cornea. Once the cornea has become opaque, visual loss is essentially irreversible.

The end stage of *Trachoma* encompassing scarring, in-turned eyelashes and corneal opacification is termed *Cicatricial Trachoma* when the opacities directly cause visual impairment.

Epidemiology

Trachoma is endemic in many countries, especially in Africa, Eritrea included.
Within a community, specific households, generally those with the least resources, provide the appropriate milieu for easy transmission of infection and for *Trachoma* to thrive. Those households at the greatest risk of *Trachoma* have young children, inadequate access to clean, germfree water and poor sanitation. These risk factors permit the facile transmission of infection primarily between siblings. Population-based observational surveys have consistently demonstrated that children with unclean faces are the most at risk of *Active Trachoma*. Presumably children with unclean faces are more likely to share ocular secretions that contain *Chlamydia tracomatis* by direct contact, shared clothing or towels, or by flies. These children will be repeatedly inoculated and infected. Because repeated infection is the stimulus for inflammation, it is these children who are more likely to progress to develop cicatricial disease and blindness.

Bacteriology

Before discussing in more detail the elimination strategy and ways of treating *Trachoma*, we must have a closer look to the bacteriology of *Chlamydia trachomatis*.
Chlamydia trachomatis are round cells between
0,3 and 1 micrometer in diameter depending on the replicative stage. The envelope surrounding the cells includes a trilaminar outer membrane that contains lipopolysaccharide and proteins similar to those of Gram-negative bacteria.

A major difference is that *Chlamydiae* lack the thin peptidoglycan layer between the two membranes. They are obligate intracellular parasites and have not been grown outside eukaryotic cells. The genom is one of the smallest among *eurokaryotes* and lacks gens for amino acid synthesis. *Chlamydia trachomatis* has ribosomes and is able to carry out the common energy production pathways of other bacteria.

The replicative cycle of *Chlamydiae* involves two forms of the organism: a small, hardy infectious form termed the *elementary body* and a larger fragile intracellular replicative form termed the *reticulate body*. The major difference between those two is the extent of cross-linking of the major outer membrane protein. The cycle begins when the *elementary body* attaches to unknown receptors on the plasma membrane of susceptible target cells, usually columnar or transitional ephitelial cells. It then enters the cell in an endocytotic vacuole and begins to process of covering to converting to the replicative *reticulate body*. As the *reticulate bodies* increase in number, endosomal membrane expands by fusing with the lipids of the Golgi apparatus eventually forming a large inclusion body. After 24 to 72 hours, the process reverses and the reticulate bodies reorganize and condense to yield multiple elementary bodies. The endosomal membrane then either disintegrates or fuses with the host cell membrane, releasing the elementary bodies to infect adjacent cells. The metabolic changes are incompletely understood, but involve protein synthesis and modification of membrane proteins between the monomeric and cross-linked state. *Chlamydia trachomatis* also inhibits *Apoptosis* of epithelial cells, thus enabling completion of its replicative cycle.

Elimination of Trachoma

The World Health Organisation (WHO) in partnership with Ministries of Health, National Health Agencies and non-government organizations have committed to the Global Elimination of Trachoma by 2020 (GET 2020).

The mainstay of this program is the so called SAFE strategy: **S**urgery for *Trichiasis*, **A**ntibiotics (Azithromycine) for active disease, **F**acial cleanliness and **E**nvironmental improvements. The SAFE strategy recommends a range of interrelated primary health care interventions to control *Trachoma*. The most pressing intervention is to establish surgical programs that can delay or prevent the onset of blindness in individuals who have *Trichiasis*. The components A, F and E of SAFE are primary health care interventions that should be implemented at the community level and are aimed to reduce the reservoir of *Chlamydia trachomatis* and disrupt the facile transmission of infection within a community. Surgery as a stand-alone intervention is highly cost-effective, however, the cost-effectiveness of mass antibiotic treatment is up to now dependent on donated antibiotics.

Facial Hygiene

Unclean faces appear to be the final pathway for the facile transmission of *Chlamydia trachomatis*. Children with clean faces are less likely to have their faces wiped with the same cloth as their siblings, are less likely to be targets for flies and do not provide a ready source of ocular secretions to share with their siblings. Facial hygiene is a modifiable behavior that has been shown to be amenable to intervention. In villages randomised to receive face-washing promotion in addition to mass antibiotic treatment, it was noted that there was a significantly lower prevalence of *Trachiasis* and the prevalence of active disease tended to be remarkably lower. In one of Eritrean neighboring States (Sudan), after three years of the SAFE strategy, the greatest reduction in the prevalence of *Trachoma* was found in regions that had a good uptake of antibiotics and an increased number of children with clean faces. In addition and as a very effective support for promoting facial hygiene, **“Swantisept-safe”** is the right choice by using it as a water disinfectant.

Environmental Improvements

The environmental sanitation component of the SAFE strategy is a package of measures aimed at eliminating factors that encourage proliferation of flies and the spread of *Trachoma* in the environment. Many of the environmental factors addressed in studies and considered risks for high *Trachoma* prevalence are easily recognized as markers of poverty. Water supply, faecal and refuse disposal and presence of animal pens within human households are all issues that have been addressed in studies. Interventions include provision of water, latrines, refuse dumps, insecticide spray to control flies, relocation of animal pens and health education to improve personal and environmental hygiene.

Mass Antibiotics

Mass antibiotic distribution should be undertaken in concert with the F and E components of SAFE. Antibiotics aim to reduce the reservoir of *Chlamydia trachomatis* within the community. The modification of hygiene behavior in response to the F (Facial Hygiene) and E (Environmental Development) should prevent the reservoir from recurring, for without a fundamental change the prevalence of infection will eventually return to baseline. You have started **M**ass **D**rug **A**dministration (MDA) already in eight of 38 districts here in Eritrea. The World Health Organisation recommends that all members of a community receive an oral dose of *Azithromycine* annually for at least three years, if the prevalence of *Trachoma* is greater than 10% in children aged one to nine years of age. *Azithromycine* is administered as a single oral dose, which results in better compliance than the alternative treatment of topical *Tetracycline*, which must be taken for six weeks. But there is currently some uncertainty about the timing of repeat mass treatment. Although annual treatment has been favoured, some

suggest six-monthly retreatment may be more effective in the long term.
Anyhow, at this stage we think that **“Swantisept-oral”** will support Your fighting for eliminating *Trachoma* in Your country. **“Swantisept-oral”** has an extremely low potential for resistance in both *Chlamydiae* and other bacterial pathogens and a most favourable side-effect profile, more clearly: no known-side effects at all when orally taken according to our recommendations. This is vital to gain and maintain public confidence in the safety and efficacy of such an important campaign, which we hopefully might start together in due course.

Topical Antibiotic

In addition to mass antibiotic distribution, we would recommend for those people who are already infected to use regularly **“Swantisept-eye-drops”,** an antibiotic topical eye ointment, which could be produced, compounded and distributed locally here in Eritrea, more precisely in Asmara at the Fred Hollows IOL Laboratory.
Besides surgery to correct advanced stages of *Trachoma*, facial cleanliness to reduce disease transmission, environmental changes to increase access to clean, germfree water by means of **“Swantisept-safe”** and improved sanitation, antibiotic therapy (*Azithromycine, Tetracycline*), **“Swantisept-oral”** proofed to be successful and could well be supported and supplemented by the use of **“Swantisept-eye-drops”**.

Antibacterial Action of **“Swantisept”**

Besides the vast field of household drinking water treatment, **”Swantisept”** combining ion, micro and nanoparticle action, has gained its established place as a major therapeutic agent in health care as well, especially in infectious disease, including surgical, eye and skin infections.

We experienced that precious metallic particles in micro- and nanosize exhibit special physical properties which are different from both the ion and the bulk material. This makes the micro- and nanosize metallic particles, which are incorporated in **“Swantisept”**, of remarkable properties such as increased catalytic activity. **“Swantisept”** with micro and nanoparticles as a new generation of antmicrobial agent has emerged up with diverse medical applications as well ranging from **“Swantisept”-**dressings to **“Swantisept”-**coated medical devices, instruments and ointments.

Although **“Swantisept”** is famous for its excellent bactericidal or bacteriostatic effect on pathogenic microorganisms, especially *Chlamydia trachomatis*, the actions of **“Swantisept”** are not completely understood yet. But latest results confirm that **“Swantisept”** acts by combining with bacterial proteins located at the cell wall or cytoplasm which fails their functioning and results in the death of the bacteria, interfering with the way bacteria replicate their genetic material or deoxyribonucleic acid (DNA), which stops the proliferation of bacteria and results in the decreasing and disappearing of the cells, or promoting the formation of a harmful chemical called reactive oxygen species (ROS) inside bacterial cells which causes significant damage to cell structures and results in the death of the bacteria. We also know that during activity, **“Swantisept”** release precious metal ions which interact with the thiol-groups of vital enzymes, which obviously plays an essential role in inactivating the bacteria.

By using a combined approach of electron microscopy and X-ray microanalysis, the existence of **“Swantisept”** and sulfur elements in the electrodense granules and cytoplasm was detected, and we suggest that the **“Swantisept”** ion takes action in a way of penetrating through the cell membrane, reacting with the thiol-group proteins, turning the DNA into condensed form and disabling its replication ability, and finally resulting in the deaths of the bacteria.

Very recently we investigated the action mechanisms of our partly electrically generated **“Swantisept”** solution on *Staphylococcus aureus* and *Escherichia coli*. We found out that the released and activated **“Swantisept”** ions on *Staphylococcus aureus* and *Escherichia coli* bacteria to reach an active but non culturable state and eventually die.. Besides, **“Swantisept”** ions might interact with the proteins associated with the proton pump of bacterial membranes. This results in a collapse of the membrane proton gradient and a disruption of cellular metabolism and hence cell death.

Besides that, we studied the molecular bactericidal mechanism of ions released from **“Swantisept”** during use by adding submicromolar concentrations of those ions to the inside-out membrane vesicles of, for instance *Vibrio cholerae*, the cause of *Cholera*. We found that the bactericidal action of these concentrations of ions from **“Swantisept”** in *Vibrio cholerae* is not mediated by a specific target, but is due to the proton (H+) leakage occurring through virtually any **“Swantisept”** ions-modified membrane protein or perhaps through the **“Swantisept”** ions-modified phospholipid bilayer itself. The **“Swantisept”** ions-sensitive domain may be involved in gating H+ release at the cytoplasmic side of the aqueous access channel.
As to **“Swantisept”** nanoparticles, they can either directly interact with the bacteria cells by interrupting transmembrane electron transfer, disrupting/penetrating the cell envelope, oxidizing cell components, or producing secondary products (such as ROR) that cause deadly damage. We learned from experience that the antibacterial action of **“Swantisept”** nanoparticles is dependent upon the bioavailability of the **“Swantisept”** ions. But when we carried out proteomic studies of the interactions between protein and nanoparticle, we identified a number of proteins from *Escherichia coli* that bound specifically to the **“Swantisept”** nanoparticles.

The results indicated that the strong binding of **“Swantisept”** nanoparticles to tryptophanase resulted in the significant reduction of the enzyme activity, suggesting that direct interaction of **“Swantisept”** nanoparticles with enzymes might lead to impaired metabolism. Furthermore **“Swantisept”** nanoparticles show a potential to destabilize the outer membrane, and deplete intracellular adenosine triphosphate levels. This was consistent with the proteomic data which revealed that a short exposure of *Escherichia coli* cells to antibacterial concentrations of **“Swantisept”** nanoparticles resulted in an accumulation of envelope protein precursors, indicating the sissipation of proton-motive force. Although the action mode of **“Swantisept”** nanoparticles was found to be similar to that of **“Swantisept”** ions, the effective concentrations of **“Swantisept”** nanoparticles and **“Swantisept”** ions were at nanomolar and micromolar levels respectively. Definitely, **“Swantisept”** in the actual composition has multiple actions against various bacteria, *Chlamydia trachomatis* included. To some extent it may be explained why **“Swantisept”** very rarely gets resisted.

Each single **“Swantisept”** nanoparticle contains approx. 20.000 effective atoms. The particle size is generally smaller than 100 nm. Therefore, the **“Swantisept”** nanoparticles provide more active sites, which will facilitate the actions against such a lot of various microorganisms. That is because at nanoscale, **“Swantisept”** presents these remarkable unusual physical, chemical and biological properties and allows very effective use in oral application, facial hygiene and topical treatment (eye-drops) as well.

In order to tackle successfully the leading cause of infectious blindness *Trachoma* and the serious world-wide antibiotic resistance storm, **“Swantisept”** is an effective self-protecting strategy for fighting *Trachoma* in Eritrea and moreover globally.

Definitely, the intrinsic antibacterial actions of **“Swantisept”** along with the unique effects of nanosize provides a robust weapon against bacteria like *Chlamydia trachomatis* and the antibiotic storm. However, a probable cytotoxicity for mammalian cells should at this stage not to be looked down on, although by far most of the representative studies on cytotoxicity of products containing nanoparticles as being used in **“Swantisept”**, were suggested to be nontoxic under specific concentration levels. Nevertheless we thought it was essential to produce a modified **“Swantisept”** with controlled antibacterial activity (depot effect) and drastically reduced cytotoxic risks.

The MilleniumDevelopment Goals

The United Nations Millenium Development Goals, aimed at galvanising the international effort to have levels of extreme poverty by 2015, include many goals that are in keeping with *Trachoma* eradication strategies. Certain goals are particularily relevant and include eradication extreme poverty and hunger. Poverty leads to the sort of living conditions and personal and community hygiene that promotes spread of *Trachoma*. In a vicious circle, *Trachoma* may then exacerbate poverty with the additional burden of blindness. One of many possible scenarios could include a child required to be a carer for an elderly blind relative, thus denying the opportunity for an education and subsequent potential to escape the poverty cycle. Loss of workforce due to blindness is a significant burden on already strained communities and families.. This relates to the second millennium development goal´, which aims to achieve universal primary education. It is rare that children with visual impairment receive adequate schooling. The third goal is to improve gender equality and empower women . *Trachoma* affects statistically much more women than men. The fourth goal is to reduce child mortality.

The community-based Trachoma control interventions promoted by the United Nations Vision 2020, including the SAFE strategy, school health programs, women's literacy training and training of health workers to perform surgery, help empower whole communities through better sanitation, hygiene and nutrition practices. Goal seven is to ensure environmental sustainability and parallels the basic tenet of the F and E components of the SAFE strategy, which promote access to clean and germfree water by using **"Swantisept-safe"** and improvements in sanitation.
A close and trustful collaboration of National Government Authorities, Ministries, Development Organizations, Academic Institutions, Universities, Clinics, the Pharmaceutical Industry and Non–profit Initiatives like our German **"Swantisept"** could become an excellent example of how eventually a successful global partnership could have a rapid and significant impact.

Conclusion

Trachoma, poverty and all of us Eritreans, Europeans, Germans are intimately entwined and addressing makers of poverty to improve overall living standards is the definitive intervention for *Active Trachoma*. This is attested to by far the fact that *Trachoma* has been eliminated from all the developed cities in the world. Improving access to safe **"Swantisept-safe"** treated drinking water, adequate waste disposal and better housing is a constructive objective for community development regardless of the impact on *Trachoma*. Furthermore, such measures provide a useful link between **G**lobal **E**limination of ***T****rachoma* program (GET 2020) and general development programs including those addressing the Millenium Development Goals.
Overcoming poverty is a giant task that may take generations. In comparison, a new common collaboration based on Global Elimination of *Trachoma* 2020 program, seems relatively straightforward, however, it must be remembered that the SAFE strategy is available here and now at this very moment.

With political and good will and a concerted effort on the ground it is within our reach to ensure that the current generation of children here in this wonderful and unique African country Eritrea is the last generation that is at risk of the terrible, painful blinding disease *Trachoma*.