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Saving 100,000 lives from pesticide poisoning through changes in national policy

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Worldwide, there are 800,000 deaths due to suicide each year. Of these, 300,000 deaths are due to pesticide self-ingestion. Sri Lanka was once known as the suicide capital of the world when 57/100,000 population died each year. This was due to easy availability of highly toxic agrochemicals. At present the world consumption of pesticides is a staggering 2.5 billion kg. It is estimated that 25 million agricultural workers experience unintentional pesticide poisoning each year. Mortality from intentional poisoning is far worse. The global burden of pesticide suicides from 1960 to 2018 is between 14 to 15 million deaths.

Before the green revolution only 5/100,000 died due to suicide in Sri Lanka. Widespread introduction of pesticides into agricultural practice of Sri Lanka during the Green Revolution of the 1950s and 60s was soon followed by an exponential increase in the number of cases of poisoning and deaths. At the beginning of the Green Revolution when fast acting, highly toxic pesticides were used in Sri Lanka, many deaths occurred before patients got to hospital. Suicide rates increased to 27/100,000 in 1976 and after the economy opened up in 1977, the rates steeped up and plateaued at 57/100,000 per year between 1983 and 1995. This increase is more likely to be due to ingestion of less toxic, more slowly acting pesticides in the 1990s that allowed patients to reach hospital before dying at home.

Until the end of the 1980s, pesticide poisoning was not even listed amongst the 10 leading causes of hospital deaths in any Sri Lankan district. This changed markedly over the next decade, pesticide poisoning becoming the 6th most common cause of hospital deaths in Sri Lanka, while in certain districts it was listed as the leading cause of hospital deaths. Problem of pesticide self-poisoning is not only limited to agricultural districts of Sri Lanka. Examination of 37,000 death certificates issued in Kandy, which is a semi agricultural district between 1967 and 1987 revealed that 77% of poisoning deaths were due to pesticide poisoning. While in agricultural districts the situation was far worse. Analysis of injury deaths in 2003 and 2004 in the North Central Province of Sri Lanka revealed that the incidence of fatal pesticide poisoning was four times as many road traffic crashes.

It has been shown that in most cases of suicides, victims found agrochemicals within their homes.

Further, there was very little planning of suicide, in most cases less than 30 minutes. Easy availability of highly toxic pesticides and impulsive behaviour were two important contributors to the high case fatality from pesticide poisoning in Sri Lanka.

Until 1962, there had been no regulation of pesticide import in Sri Lanka. At the time, most of the pesticides were imported for Malaria control and tea industry. In 1963, the controller of imports

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and exports of Sri Lanka made the first attempt to restrict use of pesticides by limiting foreign exchange for import of agrochemicals. This decision was challenged by the importers. Concurrently, the then Department of Agriculture in an attempt to regulate agrochemicals, submitted a draft bill titled "Act on Poisons Used in Agriculture" which however did not materialize. In 1972, with the assistance from Food and Agriculture Organization (FAO), the Department of Agriculture attempted to regulate use of pesticide in Sri Lanka - this too failed. The introduction of more liberal economic policies in Sri Lanka after 1977 called for tighter regulation of pesticides. Due to open economic policies, import of pesticides increased by 240% - from 2166 tons in 1976 to 5144 tons in 1979.

Due to continuous lobbying by the Department of Agriculture, the Government of Sri Lanka finally introduced Control of Pesticides Act No 33 of 1980. This act provided for the appointment of a Registrar of Pesticides (ROP) to regulate the importation, formulation, packing, labelling, storage, sale and use of pesticides in Sri Lanka. This act also provided for the appointment of a national ten-member committee (Pesticide Technical Advisory Committee) to advice the ROP. I am currently a member of this committee.

This act made it possible to restrict use of pesticide in Sri Lanka. In the early 90, import of WHO Class I organophosphates was restricted to effect a total ban of such pesticides by 1995. In 1998 endosulfan, an organochlorine associated with status epilepticus and high mortality was banned in Sri Lanka. Restriction of these compounds was associated with a reduction of incidence of deaths from self- poisoning with pesticides without any effect on agricultural output.

South Asian Clinical Toxicology Research Collaboration (SACTRC) was established at Faculty of Medicine, University of Peradeniya in 2003. The objective of this research collaboration was to reduce deaths from pesticide poisoning in Sri Lanka. It further intended to build capacity within Sri Lanka to develop a new breed of researchers in Sri Lanka. When SACTRC started work in 2003, the overall case fatality of pesticide poisoning was an astounding 10.7%. Some individual pesticides had a case fatality exceeding 50%. I function as Research Director of SACTRC.

The commonest pesticides used in agriculture and therefore for self-harm were the organophosphorus insecticides, followed by herbicides and carbamates. Paraquat, MCPA, propanil and glyphosate are the most commonly ingested herbicides. These pesticides were imported based on their safety profile determined by the Rat LD50. Human toxicity data was not available which paved the way for some of these highly toxic pesticides to be labelled as less toxic and be rampantly used by farmers of Sri Lanka.

We at SACTRC identified that Rat LD50 values have mislead policy makers in classifying toxicity of pesticides. Therefore, we examined the case fatality ratio of different agricultural pesticides in a prospective cohort of patients presenting with pesticide self-poisoning to two clinical trial centers from April 2002 to November 2008. A single pesticide was ingested by 9,302 patients. A specific pesticide was identified in 7,461 patients; 1,841 ingested an unknown pesticide. We found a large variation in case fatality between pesticides ranging from 0% to 42%. This marked variation in lethality was observed for compounds within the same WHO toxicity classification of pesticides and for those used for similar agricultural indications. We were able, for the first time to produce human data on toxicity of pesticides. Our study demonstrated that human toxicity of pesticides was different to WHO toxicity classification which was based on rat LD50. We proposed that basing regulation on human toxicity rather than rat LD50 will make pesticide poisoning less hazardous, preventing hundreds of thousands of deaths globally without compromising agricultural needs.

In this study we found that 65% of deaths were due to three pesticides namely dimethoate, fenthion and paraquat.

Based on this data, we were able to convince the PeTAC to implement bans on dimethoate, fenthion and paraquat between 2008 and 2011 in Sri Lanka. As a result, the case fatality continued to drop.

In the process we at SACTRC managed to produce close to 50 postgraduates along with 500 publications in peer reviewed journals. We were

also able to contribute to toxicology education in Sri Lanka that helped improve medical care given to these patients.

After our initial success we continued to collect data on pesticide self-harm. Our database has prospectively collected data close 100,000 victims of self-poisoning to date. We identified a cohort of 34, 902 patients who ingested a known poison and analysed their data.

We demonstrated that deaths from pesticide self-harm continue to fall. A steady decline was seen in overall case fatality of pesticide poisoning. Overall case fatality of pesticide poisoning has declined from 10.5% during 2002 to 3.7% in 2019. This drop of case fatality is largely attributable to pesticide bans imposed by PeTAC based on data provided by SACTRC. We also found that after the bans of paraquat, dimethoate, and fenthion, profenofos, propanil, fenobucarb, carbosulfan, and quinalphos are responsible for most of the remaining deaths. These have a case fatality between 7·2-8·6% which is more than the 3.7% overall case fatality.

The World Health Organization aimed at reducing deaths from poisoning by 10% by 2020. However, Sri Lanka has been able to reduce deaths by 70%, a feast that has been achieved mainly through regulation of highly toxic pesticides available in the market. These bans have resulted in prevention of at least 93,000 suicide deaths between 2003 and 2015 in Sri Lanka. By now, these policy changes may have saved 100,000 hence the title of my talk.

Sri Lanka's Control of Pesticides Act No. 33 of 1980 is among the five inspiring and impactful laws and policies that won the Future Policy Award 2021.The Award, often referred to as the 'Oscar on Best Polices', is celebrating the most effective policy solutions that minimizes the adverse effects of exposure to chemicals on human health and the environment. This policy has contributed to one of the greatest decreases in suicide rates ever achieved in the world.

These policy changes have had significant contributions to health indices in Sri Lanka. The numbers of disability-adjusted life-years (DALYs) saved by these changes has been estimated at 3·26 million. In comparison, hip replacement saves 246 DALYs.

The annual costs for the Office of the Registrar of Pesticides in the early 2000s was about US$200 000. Considering only direct costs, each life was therefore saved at a cost of $43. The direct cost to the government per DALY is just $1·23.

We aimed at further reducing deaths from pesticide self- poisoning. Most pesticide suicides are relatively impulsive with little planning: in the absence of highly hazardous pesticides, many people would have survived their suicidal impulse, gone on to find support amongst family, community, and health services, and lived a full life. We postulated that if pesticides are kept under lock and key, suicides can be prevented.

We therefore attempted to find evidence that preventing access to pesticides by providing safe boxes would reduce deaths. We conducted a large randomized controlled clinical trial in Sri Lanka. Between Dec 31, 2010, and Feb 2, 2013, we randomly assigned 90 rural villages to the intervention group with lockable boxes and 90 to the control group.

27 091 households (114, 168 individuals) in the intervention group and 26 291 households (109 693 individuals) in the control group consented to participate. 20 457 household pesticide storage containers were distributed.

In individuals aged 14 years or older, 611 cases of pesticide self-poisoning had occurred by 3 years in the intervention group compared with 641 cases in the control group; incidence of pesticide self-poisoning did not differ between groups (293·3 per 100 000 person-years of in the intervention group vs 318·0 per 100 000 in the control group. We found no evidence of switching from pesticide self-poisoning to other forms of self-harm, with no significant difference in the number of fatal or non-fatal self-harm events involving all methods.

We found no evidence that lockable household pesticide storage reduces pesticide self-poisoning. We recommended that other approaches, particularly further removal of highly hazardous pesticides from agricultural practice, are likely to

be more effective for suicide prevention in rural Asia.

This large study required the assistance of a number of people and they are acknowledged here.

One of the remaining leading causes of death from organophosphorus insecticide poisoning is intermediate syndrome (IMS). Since there is no specific treatment, its early detection is the only way deaths can be prevented. However, there were no tools available for its early prediction. Since, Intermediate syndrome (IMS) is mediated via prolonged nicotinic receptor stimulation at the neuromuscular junction we postulated that single fiber electro myography would be a useful tool in predicting development of IMS.

Chanika Alahakoon, conducted a study to investigate whether neuromuscular junction dysfunction within the first 24 hours following exposure, quantified by jitter in single fibre electromyography, can predict IMS.

This prospective cohort study was conducted at Teaching Hospital Peradeniya. We recruited on 121 patients admitted between September 2014 and August 2016. Exposure was confirmed based on the history and red blood cell AChE assays. IMS was diagnosed in patients who demonstrated at least three out of four of the standard IMS criteria: proximal muscle weakness, bulbar muscle weakness, neck muscle weakness, respiratory paralysis between 24-96 hours post ingestion.

Respiratory failure requiring intubation occurred in 74 out of 121 patients. Of the 121 patients, 96 had repeated SfEMG testing. The odds of IMS in those with prolonged jitter was 8.94 times those with normal jitter. Prolonged jitter within 24 hours had a sensitivity of 86.2% and a specificity of 57.9% in predicting IMS. Prolonged jitter recorded with SfEMG with in 24 hours of ingestion of an OP could be used as a predictor of IMS. Use of sf EMG will enable early risk assessment and allocation of resources in Sri Lanka.

Paraquat was the most popular weedicide in Sri Lanka. It had the highest case fatality rate of all pesticides in Sri Lanka.

Worldwide, high- dose immune suppression with dexamethasone, cyclophosphamide and methyl prednisolone had been the accepted as the standard of treatment. However, the recommendation was based on a small non-randomized study. We aimed to determine whether the addition of immunosuppression to supportive care offers benefit in Sri Lankan hospitals. We performed a randomised placebo-controlled trial comparing immunosuppression (intravenous cyclophosphamide up to 1g/day for two days and methylprednisolone 1g/day for 3 days, and then oral dexamethasone 8mg three-times-a-day for 14 days) with saline and placebo tablets, in addition to standard care, in patients with acute paraquat self-poisoning admitted to six Sri Lankan hospitals between 1st March 2007 and 15th November 2010. The primary outcome was in hospital mortality.

We recruited 603 patients. Of these 299 patients met inclusion criteria and were randomised to receive immunosuppression (147) or saline/placebo (152).

Their baseline characteristics, including severity of poisoning were similar.

There were 78 in hospital deaths in the immunosuppression group and 94 deaths in the placebo group which was not significant. There was no difference in mortality at 3 months between and immunosuppression (101/147 [69%]) and placebo groups (108/152 [71%]); (Mortality reduction 2%, 95% CI: -8 to +12%). A Cox model did not support benefit from high-dose immunosuppression but suggested potential benefit from the subsequent two weeks of dexamethasone.

This trial, the largest RCT in paraquat poisoning to date, showed no benefit of high dose immunosuppression with cyclophosphamide, methylprednisolone and dexamethasone in acute self-poisoning with paraquat.

Our work has clearly shown that human lives can be saved through changes of national policy. PeTAC responded positively to data presented by SACTRC which enabled banning of highly toxic agrochemicals. This act has saved close to 100,000 lives thus far. We are lobbying with PeTAC to ban the remaining pesticides with a human case fatality

ratio of more than 5%. We believe that many more lives can be saved. We have also shown through many clinical trials that some methods of treatment, though seemingly beneficial, do not work. Safe storage of pesticides in lockable boxes though attractive as a method of suicide prevention does not work. Likewise, we were able to produce evidence that immunosuppression does not prevent death from paraquat self-poisoning and this method of treatment has now been abandoned. Intermediate syndrome can be predicted early after poisoning with organophophorus compounds and use of SF EMG should be used to identify and risk stratify patients poisoned with organophosphorus insecticides. This prediction will enable allocation of scare resources in poor countries while also saving many lives.