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Original Article

Visible Deformity after HD (Leprosy) Chemoprophylaxis among Tribal People in India: Quantitative Analysis of Data Extracted from Published Sources

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This is a quantitative analysis of data concerning visible deformity among newly diagnosed Hansen's disease - HD (leprosy) patients in Dadra Nagar Haveli, India, before and after the introduction of chemoprophylaxis. Chemoprophylaxis was introduced on 1 April 2015 and consisted of a rifampicin dose >10 mg/kg for contacts of nearly all "primary" patients who were newly diagnosed from 1 April 2013 until 2017. The population had repeated door-to-door surveys in the two years before the introduction of chemoprophylaxis. Data was extracted from published sources. The variation in the annual number of newly diagnosed HD patients with visible deformity in this population in any given year was predictable to the extent of over 90% by the number of contacts in this population who had received chemoprophylaxis in the preceding year ($p = .0002$, $R^2 = 0.9132$). The population incidence rate of newly detected visible HD deformity at HD diagnosis increased substantially, from <2/million population/yr during 2010 to 2014 to >60/million population/yr in 2016, the year following the 2015 introduction of chemoprophylaxis. The evidence suggests that brief chemoprophylaxis among asymptomatic contacts of newly diagnosed HD patients was an important factor in the causation of visible deformity among newly diagnosed HD patients in this population. Biological plausibility is discussed. By contrast, the frequency of visible HD deformity typically declines between the start and end of full MDT treatment backed by a package of nerve function monitoring and holistic care. Consequently, it is recommended that the underlying biology of visible deformity after brief chemoprophylaxis be elucidated further by non-human experiments before exposing more people in endemic countries to the risks of brief chemoprophylaxis. This will help protect the limbs and eyes of family members and other contacts of persons who experience(d) HD.

Keywords: Chemoprophylaxis, Deformity, Neuritis, Leprosy, Hansen's Disease

Introduction

Prevention of visible deformity is a central goal of HD (leprosy) control. Brief chemoprophylaxis among people in endemic areas is assumed to be safe, based largely on claims from chemoprophylaxis experiments at sites including

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Dadra Nagar Haveli (DNH), India (Barth-Jaeggi et al 2016, Steinmann et al 2018, Richardus et al 2021). However, in a separate prospective study in Bangladesh an elevated risk of new nerve function impairment had been demonstrable among HD patients six to 24 months after they were started on multi-drug treatment - MDT (Croft et al 2000). 85% of the said impairment occurred through "silent" neuropathy without signs of inflammation. In well-run programmes MDT is accompanied by regular monitoring of nerve function, and prompt anti-inflammatory treatment when needed. Such precautions have not generally accompanied brief chemoprophylaxis with anti-microbials. Nevertheless, the population incidence rate of visible HD deformity at HD diagnosis is frequently recorded and reported. Consequently, the relationship, if any, between the number of people who received brief chemoprophylaxis and the subsequent population incidence rate of visible HD deformity at HD diagnosis can be analysed.

Whenever a population in an endemic area is rarely screened, a backlog of previously undiagnosed visible HD deformity accumulates. This backlog tends to obscure any marked changes in the incidence rate of newly detected visible HD deformity at diagnosis, following the introduction of interventions such as chemoprophylaxis. DNH fortunately had repeated door-do-door surveys in the years preceding the introduction of chemoprophylaxis, examining as many as 80% of the entire population in a year. Consequently, the said backlog was reduced to near zero. This facilitated analysis of the following "first null hypothesis":

There was no relationship in DNH between the number of contacts in the population who received chemoprophylaxis in one year and the number of persons in the same population with newly detected visible HD deformity at HD diagnosis during the following year.

Further, in order to weigh the possible obscuring or confounding effect of any remaining undiagnosed backlog, or any temporal change in methods or context, the reported cumulative incidence rate during the period 1 April 2015 until the end of the study intake in FY2017 was compared between two contemporaneous groups in this population:

a) 42,333 contacts examined for signs of HD during FY2015 to FY2017 before being considered for chemoprophylaxis.

b) The remaining members of the population of DNH who were not so examined but among whom nevertheless the number of persons with newly detected visible HD deformity at HD diagnosis for the same period FY2015 to FY2017 was recorded and reported.

According to this "second null hypothesis", if the said backlog entirely explains the cumulative period incidence rate of newly detected visible HD deformity at HD diagnosis, then the said cumulative incidence rate during 2015 to 2017 should be very similar or identical in the said groups a) and b). Likewise, any differences arising from temporal changes in methods or context should occur randomly in both groups a) and b) above, leaving a similar or equal cumulative period incidence rate of newly detected visible HD deformity at diagnosis for 2015-207, between the said two groups.

Materials and Methods

Definitions used in the study are:

(i) *Chemoprophylaxis* – Single dose rifampicin at >10 mg/kg for contacts aged 2 years or more, who were considered by health workers to be free from HD and TB. In order to avoid immediate reinfection of the contact after chemoprophylaxis, at least four weeks were allowed after the start of MDT in the presumed source of infection, the "index"

patient, before giving chemoprophylaxis (Barth-Jaeggi et al 2016).

(ii) *Contacts* - Household, neighbour and social contacts of primary HD patients diagnosed <2 years before the start of the field work and throughout the study period were eligible for inclusion (Barth-Jaeggi et al 2016).

(iii) *Disease* – Change from normal structure and function with clinically detectable signs. The reported frequency of new HD is directly proportional to the clinical experience and expertise of health professionals, and the frequency with which an individual in the population is examined (Jesudasan et al 1984). The greater the interval between examinations, the greater the opportunity for self-healing or for visible deformity to occur between examinations.

(iv) *Infection* - Invasion of the body tissues of a host by an infectious agent, whether or not it causes disease. In the context of HD (leprosy) it refers to changes in the host attributable to infection by the bacilli. In the 1970s and even during the 1990s such changes were sometimes detected by the lymphocyte transformation test. It was frequently positive in endemic areas, eg., positive in 50% of expatriates/immigrants to the area within one year of stay, and in 88% of local health staff at an HD outpatient clinic there (Godal & Negassi 1973). Accordingly, as many as half of all residents or contacts in an endemic area may have been infected with the bacilli. However, in many endemic areas less than 0.01% (10 in 100,000) of the population/year has been newly detected to show physical signs of disease (WHO, Global Leprosy update 2015).

(v) *Newly diagnosed/detected visible HD deformity* - Persons newly diagnosed/detected to have HD with visible deformity at diagnosis.

(vi) *Primary patients* – HD patients newly diagnosed since 1 Apr 2013. According to the LPEP study protocol (Barth-Jaeggi et al 2016), patients diagnosed <2 years prior to the start of the field work and patients newly diagnosed during the study period were included as primary (index) patients. Index patient is not the term used here, because the true main source of infection may be someone other than the primary patient. Reinfection of a genomically susceptible contact cannot be ruled out in an endemic area once the tissue concentration of an anti-microbial declines in the contact. Reinfection of lepromatous (LL) index patients even long after MDT cannot be ruled out.

(vi) *Virulence* – the ability of a pathogen to cause damage or signs of disease in a host.

Methods

The data used in the quantitative analysis here comes solely from published reports. Published reports have been open to public scrutiny.

A National Sample Survey in a sample of the DNH population had been done door-to-door in 2010-11 with expert backing and verification (Katoch et al 2017). Zero visible deformity was found among 35 newly diagnosed HD patients, including 3 patients with MB HD, among the population of 13,660 persons in Dadra town, part of DNH. This is interesting background information. It will not be relied on except to examine inconsistency, if any, with the incidence rates of new visible HD deformity reported by the routine control programme.

Active case-finding including door-to-door surveys were done by the national programme in financial years (FY) 2013 and 2014 (NLEP reports). In FY2013 of 257,676 persons examined, zero were found to have visible deformity at the time of HD diagnosis. In FY2014, of 341,620 persons examined, two persons were newly diagnosed with HD and visible deformity (NLEP reports). Neither of these findings is inconsistent with the

findings of the National Sample Survey in Dadra town (Katoch et al 2017).

The leprosy post-exposure prophylaxis (LPEP) chemoprophylaxis administration began in 2015 at the DNH site (Steinmann et al 2018, Richardus et al 2021). According to the LPEP protocol (Barth-Jaeggi et al 2016) the study was intended to demonstrate a reduction in case detection rates of HD. For quality data collection and analysis, expert external guidance was provided plus local data entry staff. Otherwise, local programme staff remained in place continuing the same criteria and methods. Chemoprophylaxis consisted of a single dose of rifampicin at roughly 10mg or more/kg body weight given to consenting and eligible household, neighbour and social contacts of newly diagnosed HD patients, excluding contacts aged under two years. Health staff and recipients of chemoprophylaxis were informed that chemoprophylaxis would ensure some protection against HD.

Contacts of primary patients from the three years 2013 to 2015 were screened in 2015 (Steinmann et al 2018). Those eligible and willing were given chemoprophylaxis starting from 1 April 2015 (Steinmann et al 2018). Thereafter contacts of newly diagnosed primary patients were likewise screened and evaluated for chemoprophylaxis. Contacts who received chemoprophylaxis and were subsequently diagnosed with clinical signs of HD were not deported from the area. They continued in the area and themselves met the protocol criteria for "primary" patients, or "index" patients in the terminology of the LPEP study (Barth-Jaeggi et al 2016). In FY 2015 to part of FY 2017, within the LPEP study, 42,333 contacts of patients newly diagnosed since 1 April 2013 were screened before chemoprophylaxis (Richardus et al 2021). Their average age was 15 years. Zero visible deformity was found among them. This will be used later to help estimate the population incidence rate of visible HD deformity. It will also be used to evaluate the "second null hypothesis" mentioned above.

A total of 23,417 contacts of primary HD patients who had been newly diagnosed from FY2013 to 1 July 2017 was given chemoprophylaxis between 1 Apr 2015 and 1 July 2017 (Steinmann et al 2018). The number of primary patients reported by National Leprosy Eradication Programme of India (NLEP) each financial year (FY) is shown in Table 1.

Linear regression (MS Excel Data Analysis) was used to test the null hypothesis of no relationship between the number of contacts given chemoprophylaxis in one year and the number of newly diagnosed patients with visible deformity in the following year.

Binomial probability was used to test the hypothesis that the cumulative incidence of newly diagnosed HD with visible deformity in the population during FY2015 to FY2017 was the same with or without chemoprophylaxis. P = e^-Np where N is the number of persons in a sample, P is the probability of finding zero visible HD deformity among N persons and p is the probability of every person in the population showing visible HD deformity.

Results

The number of contacts who received chemo-prophylaxis in each year is shown in Table 2, assuming equal distribution of 23,714 contacts (Steinmann et al 2018) who were given chemo-prophylaxis across the 1447 primary patients reported in FY 2013 to FY2016 (NLEP reports). These 1447 primary patients included the 1398 primary patients registered for the LPEP study until 1 July 2017 (Steinmann et al 2018). Table 2 also shows the number of newly diagnosed HD patients with visible deformity in each year.

Table 1: Newly diagnosed "primary" HD patients reported in each financial year (FY), and total population

	2012	2013	2014	2015	2016
PB (paucibacillary)	283	223	204	312	283
MB (multibacillary)	85	97	114	113	101
Census population projection	387000	409000	431000	452000	483000

Data sources: NLEP reports (FY2012-2016), Census 2011 population projections (2019)

Table 2: Number of newly diagnosed HD patients with visible HD deformity and number of contacts given chemoprophylaxis in each financial year, FY2010-17.

	2010	2011	2012	2013	2014	2015	2016 5 qs*	2017 part
Newly diagnosed patients with visible deformity	1	0	0	0	2	8	37	7
Total contacts given chemo-prophylaxis	0	0	0	0	0	17203	6214	6878

*Five quarters 1 Apr 2016 to 1 July 2017 as reported by the LPEP study (Steinmann et al 2018)

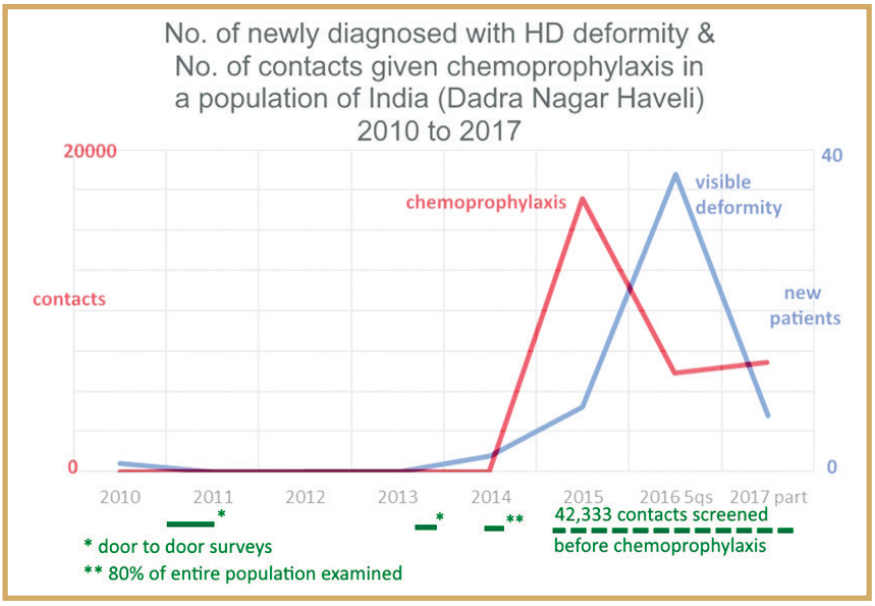

Fig. 1: Numbers of contacts who received chemoprophylaxis and numbers of newly diagnosed HD patients with visible deformity at diagnosis, in each year FY2010-17.

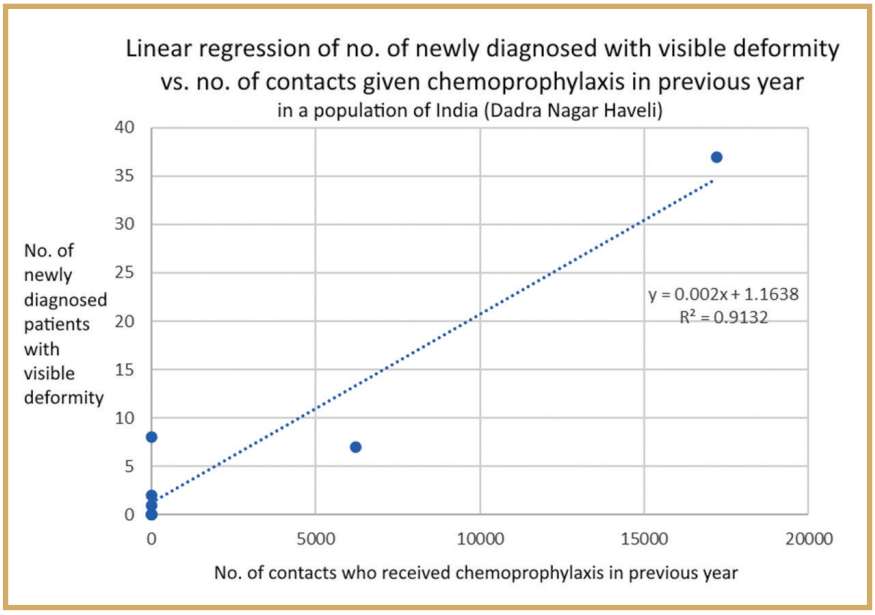

Fig. 2 : Linear regression, test for absence of a relationship between the number of contacts administered chemoprophylaxis in a given year (independent variable) and newly diagnosed patients with visible deformity in the respective following year (dependent variable).

47 primary patients with visible deformity were reported by Steinmann et al (2018) for the period 1 Apr 2013 to 30 June 2017. This includes the 2 newly diagnosed patients with visible deformity reported by the NLEP in 2014 (before the introduction of chemoprophylaxis on 1 April 2015), and the 8 newly diagnosed patients with visible deformity reported by NLEP in FY2015. That leaves 37 newly diagnosed and with visible HD deformity during 1 Apr 2016 to 30 June 2017, using the data reported by Steinmann et al (2018).

Figure 1 is a plot of the numbers in Table 2.

Active case-finding was done throughout the study period FY2015-17 and earlier from FY2010 onwards, including large-scale door-to-door surveys in 2013 and 2014.

The following "first null hypothesis" was formally tested:

There is no relationship between

a) the number of contacts given chemoprophylaxis in a particular year, and

b) the number of HD patients newly diagnosed and with visible deformity in the respective following year.

The numbers from Table 2 for the years 2010 to 2017 as depicted graphically in Figure 1 are also used for the linear regression depicted in Fig. 2.

The fitted linear regression was: y = 0.002x + 1.1638 where y is the dependent variable, number of newly diagnosed patients with visible deformity and x is the independent variable, number of contacts given chemoprophylaxis in the previous year.

The overall regression is statistically significant (p = .0002); R^2 = 0.9132, F (df regression 1, df residual 6) = 63.138, Sum of squares regression 1012.6437, SS residual 96.2313.

In this population, contrary to the "first null hypothesis" above, variation in the number of newly diagnosed persons with visible deformity in any given year is predictable to the extent of over 90% (p= .0002, R^2 = 0.9132) by the number of contacts given chemoprophylaxis in the preceding year. The more contacts given chemoprophylaxis in a given year x, the more newly detected persons with HD in this population were found with visible deformity at diagnosis in year x+1. Similarly, the fewer contacts given chemoprophylaxis in a given year x, the fewer newly detected with HD in this population were found with visible deformity at diagnosis in year x+1.

42,333 contacts were screened from 2015 to 2017 before being considered for chemoprophylaxis (Richardus et al 2021). Zero visible deformity was found among them. Their average age was 15 years. They had contributed 634,995 person-years during which zero visible deformity had occurred. Accordingly, the population incidence rate of newly diagnosed visible HD deformity among persons without chemoprophylaxis is calculated to be <1.6/million population/year. Since contacts have a higher risk of HD than non-contacts, this is likely to be an over-estimate of the population incidence rate of newly diagnosed visible HD deformity without chemoprophylaxis.

Was the cumulative population incidence rate of newly detected visible deformity at HD diagnosis identical with or without chemoprophylaxis, during a given time period? The following "second null hypothesis" was evaluated:

The cumulative incidence rate of newly detected visible HD deformity during the period 2015 to 2017 was the same among

a) *42,333 contacts screened during 2015 to 2017 before being considered for chemoprophylaxis and*
b) *the remaining population of no more than 500,000 persons residing in DNH during 2015 to 2017.*

After the introduction of chemoprophylaxis on 1 April 2015 (Steinmann et al 2018), 52 persons with newly detected visible HD deformity were reported in the population of no more than 500,000 residents (Richardus et al 2021, and Census of India 2011 population projections 2019). A total of 54 "primary" patients with visible deformity was reported by Richardus et al (2021) for the period 1 Apr 2013 until the end of the study intake, in FY2017. This includes the 2 newly diagnosed patients with HD and visible deformity reported by the NLEP in 2014. None of the HD patients newly detected in 2013 was reported to have visible deformity at diagnosis. Accordingly, the remaining 52 newly diagnosed patients with HD and visible deformity were all newly detected and reported during the period 1 April 2015 until the end of the study intake (Richardus et al 2021). Applying 52/500,000 as the minimum expected cumulative incidence rate of newly diagnosed visible deformity among 42,333 contacts screened during the same period 2015 to the end of the study intake but before they were considered for chemoprophylaxis, the binomial probability of finding the observed zero visible HD deformity among these 42,333 contacts is calculated to be p = .012 (ie., p<.05) Therefore, the null hypothesis above is rejected. In other words, there was a material difference after the introduction of chemoprophylaxis between the said groups a) and b) above, in the cumulative population incidence rate, during the said period, of newly detected visible deformity at HD diagnosis.

This particular finding is merely corroborative of the demonstrable direct relationship between chemoprophylaxis and the subsequent incidence rate of newly diagnosed visible HD deformity illustrated in Figs. 1 and 2. It suggests that the newly diagnosed visible HD deformity in DNH after the introduction of chemoprophylaxis on 1 April 2015 is unlikely to be due to a backlog of previously undetected visible HD deformity or to

any temporal changes in methods or criteria.

The national programme (NLEP) with intensive case-finding including door-to-door surveys had reported only one newly detected patient with visible deformity in 2010, and only two such patients in 2014, out of the entire population of DNH (NLEP reports 2010-2016). Given the census-projected resident population in each year, (Census of India 2011 population projections 2019) this amounts to an annual average of less than 2/million population/year newly diagnosed visible HD deformity in DNH, during the years 2010 to 2014. In 2016, the year following the introduction of chemoprophylaxis, the population risk of newly diagnosed visible HD deformity in this population rose to 61.3 per million population/yr. This is based on Steinmann et al (2018). 47 primary patients were newly diagnosed and with visible deformity between 1 Apr 2015 and 30 June 2017. This included 2 such primary patients in 2014 and 8 in 2015 reported by NLEP. That leaves 37 newly diagnosed and with visible HD deformity during 1 Apr 2016 to 30 June 2017 as reported by Steinmann et al x 4/5 to correct for 5 included quarters / 483000 official census-projected population in 2016 x 10^6 = 61.3/million population/year. Sensitivity analysis of R^2 taking 4/5 x 37 incident cases with visible deformity in FY2016 and 14 cases in FY2017 would yield an even higher R^2 value and smaller p value (R^2 = 0.9337, p=.00002), with a regression equation y = 0017x + 2.01.

Accordingly, the observed increase in the annual risk of newly diagnosed visible HD deformity was (61.3/ <2 =) >30 times, or >3000% compared to FY2010-2014.

In brief, the evidence indicates that the introduction of chemoprophylaxis for contacts was followed by a substantial increase in the population risk of visible deformity detected by the routine programme about a year after the administration of chemoprophylaxis, and attributable largely to chemoprophylaxis. At its highest point in 2016 this increase was large, of the order of >3000% relative to the preceding 2010 to 2014 period.

Discussion

Variation in the annual number of newly diagnosed persons with HD and visible deformity in any year, as shown above, is explicable to the extent of over 90% (p= .0002, R^2 = 0.9132) by the number of contacts given chemoprophylaxis in the preceding year. The population risk of newly diagnosed visible HD deformity, as defined at the start, was <2/million population/year during FY2010 to FY2014. After the introduction of chemoprophylaxis in 2015 it rose to >60/million population/year in FY 2016. This was an increase of >3000%. Further, a proportionate relationship was observed, as displayed in Figs. 1 and 2. The greater the notional "population intensity" of chemoprophylaxis, that is the more of the population who received chemoprophylaxis in a year, the greater was the subsequent boost in population risk of newly diagnosed visible HD deformity. This is analogous to a "biological gradient" (Hill 1965) with exposure being the "population intensity" of chemoprophylaxis and outcome being the population incidence rate of visible deformity at diagnosis. The high R^2 value taken together with the zero visible HD deformity among the 42,333 pre-chemoprophylaxis contacts during the same period FY2015 to FY2017 suggests that chemoprophylaxis was an important factor in the causation of newly diagnosed visible HD deformity in this population. Biological plausibility (Hill 1965) is discussed later.

Nerve function impairment in HD occurs through silent neuropathy in 85% of cases, without clinical signs of inflammatory "reaction" or neuritis (Croft et al 2000). However, visible deformity can also be preceded by neuritis. To that extent it is interesting to note the number of HD patients reported to show signs of neuritis in each year in

DNH: none in FY 2010 to 2012 inclusive, 6 in FY 2013, none in FY 2014, 25 patients in FY 2015 and 38 patients in FY 2016 (NLEP reports 2010-2016). This data does not contradict the observed boost in visible deformity among newly diagnosed HD patients from FY2015 onwards, following the introduction of brief chemoprophlyaxis on 1 April 2015 (Steinmann et al 2018).

Further, while the chemoprophylaxis study was confined to DNH, other states in India were under similar or identical national HD control policies and practices apart from chemoprophylaxis. Neighbouring Indian states of Maharashtra and Gujarat were under no chemoprophylaxis in FY2015. They showed no such dramatic boost in newly detected visible HD deformity in 2016 (NLEP reports). The reported rate of newly detected HD with visible deformity in 2016 was only 3.68/million population in Maharashtra, only 2.30/million population in Gujarat and only 3.94/million population on average across the whole of India. Accordingly, DNH before chemoprophylaxis with intensive door-to-door case-finding and an average of <2/million population/yr newly detected visible HD deformity compared favourably with the Indian national average. After the introduction of chemoprophylaxis in 2015 the said rate in DNH increased, as shown above, to >60/million population/year in 2016. This was much higher than in pre-chemoprophylaxis DNH, and much higher than in the neighbouring comparator states of Maharashtra and Gujarat. This too suggests a causal relationship between population intensity of brief chemoprophylaxis and subsequent population incidence rate of visible deformity at diagnosis.

The underlying biological explanation for the relationship between brief chemoprophylaxis and excess visible deformity detectable around a year thereafter deserves elucidation. This would preferably be by use of in vitro or animal studies rather than human experiments. Protection of human safety is not optional. Such protection seems especially important in endemic areas such as DNH where 99% of newly diagnosed HD patients belong to indigenous tribes (NLEP reports) and illiteracy has not yet been eradicated.

Biological plausibility :

Plausible underlying mechanisms include a) disruption of natural self-healing in infected asymptomatic contacts, partly by killing of some *M. leprae* with consequent disruption of the protective feedback loops of the vit D-induced cathelicidin system in infected perineural macrophages (Mandal et al 2015, Singh et al 2018, Hemshekhar et al 2018, Rowe-Magnus et al 2019) resulting in damaging perineural concentrations of reactive oxygen species (Medeiros et al 2016). This is analogous to disruption of the balance between an accelerator and a brake in a car. Signs can include type 1 “reaction” (Sugawara-Mikami et al 2022). Some drugs also reduce vitamin D levels by inducing hepatic enzymes, e.g., the enzyme CYP3A4 (Williamson et al 2013), further disrupting the cathelicidin system. Dead bacilli and viable bacilli evoke notably different host responses (Marolia & Mahadevan 1987, Medeiros et al 2016, de Souza et al 2022, Brugger et al 2023). Live perineural *M. leprae* can maintain homeostasis eg., by altering expression of host proteins (Salgado et al 2018) and inhibiting apoptosis (Rodrigues et al 2010). All of the above is consistent with anti-microbials increasing the risk of nerve damage and visible HD deformity (Radhakrishna & Nair 1987, Solomon et al 1998), especially if quarterly nerve function monitoring is omitted. b) Stressors such as anti-microbials can induce efflux pumps in previously dormant *M. leprae* (eg., MFS transporters of the virulence factor phenolic glycolipid 1 (PGL-1) to the surface of the bacillary cell membrane) (Machado et al 2018), with PGL-1 boosting inducible Nitric Oxide Synthase in perineural macrophages followed by Nitric Oxide damage to mitochondria in

axons (Madigan, Cambier et al 2017, Madigan et al 2017). In the key animal model of HD nerve damage, the infected armadillo (Pena et al 2022), cMAP (compound muscle action potentials) can become impaired within 4 months, followed by complete loss of conduction with deformity appearing within 12 to 24 months. This timeline is similar to the time lag observed in DNH between the introduction of chemoprophylaxis and the observed boost in newly detected visible HD deformity at diagnosis. c) Contacts who have covert LL HD with few or no signs can be mistaken for healthy contacts and be given brief chemoprophylaxis, delaying diagnosis of LL HD. Such missed LL HD cases not only can shed astronomical numbers of viable bacilli (Davey and Rees 1974), but also are at elevated risk of visible deformity before eventual diagnosis.

MDT or brief chemoprophylaxis?

Bacilli are killed by MDT (multi-drug therapy) too. Is the risk of visible deformity increased by MDT? Brazil monitors the frequency of visible deformity not only at diagnosis but also in a proportion of patients at the end of MDT. The frequency of visible deformity at the end of 6 to 12 month-MDT in Brazil (eg., 8.43% during 2023) is lower than the frequency of visible deformity among newly diagnosed patients during the preceding year (11.47% during 2022) (Ministério da Saúde 2024). In brief, MDT together with its accompanying package of care in Brazil reduces the risk of visible deformity. MDT usually involves monthly contact between the patients and the health service for at least 6 to 12 months. Brazil encourages regular monitoring of nerve function during MDT and to an extent even after MDT. Such regular monitoring enables prompt anti-inflammatory treatment at the first sign of nerve function impairment. This helps prevent visible deformity. Only patients who reside at a great distance from the nearest health care provider, such as in the Amazon regions, might unavoidably have infrequent contact with the health services. Nevertheless, Brazil's rejection of brief chemoprophylaxis and its reliance instead on full MDT with proper care seems scientifically sound. Further, adequate treatment and holistic care respect ethics and human rights.

The largest randomised controlled trial (RCT) of chemoprophylaxis to date, used double dose rifampicin (roughly 20 mg/kg) and was carried out in Comoros/Madagascar. The data from this "PEOPLE" trial showed 42 incident MB (multibacillary) cases in the "household contacts" chemoprophylaxis arm compared to only 27 in the non-chemoprophylaxis control arm within three years, despite an equal 18 incident cases of all types of HD occurring in each arm during the initial year of door-to-door follow-up (Hasker et al 2024). Although the frequency of visible deformity was not disclosed for any arm of this RCT, persons with MB HD are known to have a much greater risk of deformity than do asymptomatic persons, and even a twelve times greater risk of new nerve function impairment than do persons with PB HD, typically detected six to 24 months after the start of anti-microbials (Croft et al 2000). 85% of nerve damage occurs silently, without signs of inflammation (Croft et al 2000). Therefore, an excess risk of visible deformity in the household contacts chemoprophylaxis arm cannot be ruled out.

In Kiribati, chemoprophylaxis for household, neighbour and social contacts of newly diagnosed HD patients was introduced after two years of intensive case finding, 2015-2017. This is likely to have detected most or all of any backlog of undiagnosed children with visible HD deformity. Following the introduction of chemoprophylaxis in Kiribati in 2018, the number of newly diagnosed children with visible deformity at HD diagnosis exceeded 20/million children/year during the six years from 2018 to 2023 (calculated from WHO, Global Leprosy (Hansen Disease) updates, 2019-

2024), while the number of newly diagnosed child MB patients was greater in 2022 than in 2017 (Campbell et al 2024). A similar Pacific Island population, Federated States of Micronesia, which avoided chemoprophylaxis during those same years 2018-2022, reported zero incidence of visible HD deformity among newly diagnosed children (WHO, Global Leprosy (Hansen Disease) updates (2019-2024)). Under-detection of visible deformity in children of school age is less likely than other kinds of under-diagnosis in HD, suggesting a real difference between these two Pacific Islands in the risk of visible HD deformity among children.

Accordingly, based on the evidence so far, chemoprophylaxis in HD cannot be presumed safe. Further, unlike the body's vitamin D- induced cathelicidin anti-microbial peptide system, and unlike vaccines, brief chemoprophylaxis only temporarily maintains effective anti-microbial concentrations in tissues, and so offers no lasting protection against HD. Reinfection after chemoprophylaxis is possible wherever sources of infection remain. Given the boosted risk of visible deformity with brief chemoprophylaxis, ethical informed consent requires full disclosure of the risks to "index" patients and prospective chemoprophylaxis recipients. Further, trials or practices designed or sponsored by affluent countries need to maintain the ethics standards codified in those countries especially if the trials are carried out in non-affluent endemic countries. For example, trials sponsored by EU (European Union) entities need to respect well-codified EU ethics standards. The Nuremberg code on human experiments states, *"The scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject."*

There are other concerns about post-exposure prophylaxis. Researchers have been discovering different mechanisms and multiple pathways leading to rifampicin resistance in mycobacteria. For example, rifampicin can increase the rate of mutations in mycobacteria (Cebrián-Sastre et al 2023). This can lead to enhanced levels of drug resistance and bacillary survival in HD and TB. Further, a specific hypermutable bacillary phenotype was found to provide an efficient response to rifampicin, leading to high rates of mycobacterial survival.

Mutation to drug resistance in mathematical terms is a discontinuity, and therefore little reliance can be placed on the presumed remoteness of the threat. Pilot studies of brief chemoprophylaxis with rifampicin at various sites in Brazil starting in 2016 failed to show the anticipated 10%-15%/ year decrease in new cases (Barth-Jaeggi et al 2016, Richardus et al 2021). Instead, some sites such as Araguaína even showed an increase in new MB HD - from 45 cases in 2016 to 86 in 2019, and visible deformity at HD diagnosis - from <5 cases in 2016 to >25 cases in 2019. (Centro Nacional de Inteligência Epidemiológica e Vigilância Genômica, Hanseníase, 2025). Such unanticipated outcomes together with concerns among Brazilian experts about increasing the frequency of rifampicin-resistant mycobacteria in TB and HD contributed to the Brazilian Ministry of Health not recommending single dose rifampicin post-exposure prophylaxis since 2020.

Several projects using competent diagnosis and adequate anti-microbial treatment of LL (lepromatous) HD demonstrated relatively rapid decline, as much as 20%/year, in the incidence rate of HD including MB HD and LL HD (Tonglet et al 1989, Smith & Richardus 1993, Li et al 1995,

Norman et al 2006, Khang et al 2019, LEP/KPS team 2024, Hernandez-Bojorge et al 2024). Such demonstrably achievable rapid decline might well be accelerated by MIP vaccine for highly bacillated patients, alongside MDT of adequate duration with holistic care. Newer vaccines too might prove useful. Therefore, the need for human experiments with chemoprophylaxis is not pressing. There is no pressing need to place at risk the limbs and eyes of family members and other contacts of HD patients in endemic countries. Competent diagnosis followed by MDT of adequate duration with regular monitoring of nerve function and comprehensive patient care appears to be clinically and epidemiologically more effective and safer than brief chemoprophylaxis.

Conclusions

Chemoprophylaxis for contacts of newly diagnosed HD patients in this Indian population appears to be an important factor in causing a substantial increase in risk of newly detected visible HD deformity at diagnosis during the following year. Consequently, it is recommended that the underlying biology of visible deformity after brief chemoprophylaxis be elucidated further by non-human experiments before exposing more people in endemic countries to the risks of brief chemoprophylaxis. This will help protect the limbs and eyes of family members and other contacts of persons who experience(d) HD.

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