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MAJOR ARTICLE

The Cumulative Impact of Harm Reduction on the Swiss HIV Epidemic: Cohort Study, Mathematical Model, and Phylogenetic Analysis

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Background. Human immunodeficiency virus (HIV) transmission among injecting drug users (IDUs) is increasing in the United States due to the recent opioid epidemic and is the leading mode of transmission in Eastern Europe.

Methods. To evaluate the overall impact of HIV harm reduction, we combined (1) data from the Swiss HIV Cohort Study and public sources with (2) a mathematical model expressed as a system of ordinary differential equations. The model reconstructs the national epidemic from the first case in 1980 until 2015. Phylogenetic cluster analysis of HIV-1 pol sequences was used to quantify the epidemic spillover from IDUs to the general population.

Results. Overall, harm reduction prevented 15 903 (range, 15 359–16 448) HIV infections among IDUs until the end of 2015, 5446 acquired immune deficiency syndrome (AIDS) deaths (range, 5142–5752), and a peak HIV prevalence of 50.7%. Introduction of harm reduction 2 years earlier could have halved the epidemic, preventing 3161 (range, 822–5499) HIV infections and 1468 (range, 609–2326) AIDS deaths. Suddenly discontinuing all harm reduction in 2005 would have resulted in outbreak re-emergence with 1351 (range, 779–1925) additional HIV cases. Without harm reduction, the estimated additional number of heterosexuals infected by HIV-positive IDUs is estimated to have been 2540 (range, 2453–2627), which is equivalent to the total national reported incidence among heterosexuals in the period of 2007 to 2015.

Conclusions. Our results suggest that a paramount, population-level impact occurred because of the harm reduction package, beyond factors that can be explained by a reduction in risk behavior and a decrease in the number of drug users over time.

Keywords: harm reduction; HIV; injecting drug use; needle and syringe exchange; opioids.

Human immunodeficiency virus (HIV) transmission via injecting drug use remains one of the leading modes of transmission in Eastern Europe and many Asian countries (eg, China, Indonesia, Iran), and it is recently re-emerging in the United States as a result of the growing heroin epidemic, which is driven by overprescription of opioid analgesics [1–3].

Despite a large body of evidence on the effectiveness of harm reduction measures to halt the spread of HIV among people who inject drugs, there is still a large heterogeneity in the estimates [4]. These measures also remain politically controversial and are far from being universally implemented and accepted [5, 6]. As a result, the harm reduction coverage is still extremely low across the world and lags behind World Health Organization (WHO) targets [7].

From the early 1980s, Switzerland experienced one of the heaviest burdens of drug addiction (mainly heroin and cocaine) in Europe, which manifested in the emergence of large open drug scenes such as the "Platzspitz" ("Needle-Park") in Zürich. This resulted in an outbreak of HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) infections in this risk group, and Switzerland had the highest acquired immune deficiency syndrome (AIDS) incidence rate in Europe in 1988 [8]. After a growing public outcry, and considering the failure of repressive measures as the main response tool, a new progressive drug policy was gradually implemented that was based on "four pillars": prevention, therapy, harm reduction, and law enforcement [9].

The main harm reduction measures included the following: (1) extensive needle-exchange programs, ie, on-site distribution at open drug scenes, pharmacies, and syringe vending machines; (2) supervised drug consumption rooms; (3) low-threshold methadone programs; and (4) since 1994, a

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supervised, injectable medicinal heroin program. In parallel, a wide-reaching "STOP AIDS" campaign was launched with a tailored message for drug users, which emphasized the HIV risk in needle sharing [10]. Furthermore, HIV-infected current and former injecting drug users (IDUs) had broad access to antiretroviral drug treatment programs [11, 12].

From the public health perspective and particularly regarding HIV transmission, those efforts proved to be a phenomenal success. Despite a relatively low cessation rate of drug use and despite the fact that the prevalence of heroin addiction remained relatively stable [13], the transmission of HIV among IDUs in Switzerland dropped from a peak of 937 new cases in 1989 to a low of 2% (9 of 519) of all new infections in 2014, hence almost eliminating HIV transmission among IDUs.

To date, a quantitative evaluation of the cumulative impact of the implemented harm reduction measures has not been performed. In this study, we combine a mathematical model with the data from the Swiss HIV Cohort Study (SHCS), the SHCS drug-resistance sequence database, national epidemiological data, and data from previous works to perform the following: (1) estimate the counterfactual HIV incidence and prevalence among IDUs in absence, or with delayed introduction, of the harm reduction measures; (2) examine the effect of discontinuing harm reduction measures when the HIV epidemic among IDUs appears as under control; and (3) estimate the cumulative effect of the implemented harm reduction measures on the spillover of the epidemic to the general population in Switzerland.

METHODS

Ethics

We obtained ethical approval from the SHCS and written informed consent from all participants.

Swiss HIV Cohort Study and the Drug Resistance Database

The SHCS is an ongoing prospective cohort of HIV-positive individuals. The study prospectively enrolled patients since 1988, and some data were retrospectively ascertained until 1981. During the biannual outpatient visits, comprehensive clinical and behavioral data are collected [14]. In addition, for more than 60% of the participants, partial *pol* sequences are available. The representativeness of the SHCS was estimated to be high, with good coverage of marginalized and hard-to-reach populations, and is particularly good for subtype B, which is the predominant subtype in Switzerland [15].

Mathematical Model

We constructed a compartmental, deterministic transmission model represented as a nonlinear system of 32 ordinary differential equations (Figure 1). The model reconstructs the epidemic from the first introduced HIV case into the IDUs population in 1980 and is numerically solved until 2015. The modeled population corresponds to all heroin users in Switzerland. The model is divided into 3 meta-strata that represent a typical progression of an addiction course: (1) "non-injectors" represent people who smoke or snort heroin; (2) "active injectors" represent populations at risk of infection with HIV by sharing injection paraphernalia; and (3) "past-injectors" represent people covered by harm reduction that are still addicted to opioids, but do not contribute to the infectious pool anymore, since they switched to snorting/smoking or are in a methadone or supervised heroin program and permanently ceased injecting in a setting that facilitates transmission. The active injectors and the past-injectors are stratified into HIV susceptible and infected. All infected IDUs start in the undiagnosed compartment and can be diagnosed either in recent, chronic, or AIDS stage, with different rates. Since 1996, diagnosed individuals can transit to a combined antiretroviral treatment (cART) treated stage, with rates that depend on the disease stage and are increasing with calendar year to reflect transition to immediate treatment. Those rates were estimated from the SHCS based on CD4 counts as a proxy for disease stage (Supplementary Table 3). Except for past-injectors, which are covered by harm reduction by definition, each compartment is mirrored by a parallel harm reduction-covered strata to which individuals transit with an average rate that represents the harm reduction recruitment rate. Because the different harm reduction layers were overlapping in time (see Supplementary Figure 1), we do not model the separate effect of each measure (methadone, needle exchange, supervised injectable heroin, etc), but we use a harm reduction "package" [7] that was introduced in 1988, which means being covered by any of the harm reduction measures versus being missed by all of them. The exception to this pooled consideration of harm reduction is the restricted methadone program, because this was the main available measure before the introduction of the package, which allowed us to disentangle its effect. We assumed that IDUs covered by harm reduction had lower HIV transmission coefficient. This transmission rate, the harm reduction package recruitment rate, and other model parameters were determined by fitting the model using negative log-likelihood-distributed error to the annual number of new HIV cases and AIDS deaths in IDUs that were reported to the Swiss Federal Office of Public Health. See the Supplementary Data for a detailed description of the model, parametrization, and sensitivity analysis.

Phylogenetic Analysis

A large maximum likelihood phylogenetic tree with 19 604 Swiss sequences and 90 994 non-Swiss background sequences was constructed as previously described [16]. Introduction events into the general (heterosexual) population that originated from IDUs were detected by extracting all clusters that comprised only Swiss sequences and had at least 1 IDU and 1 heterosexual individual. For each IDU, the tree nodes were traversed back until the cluster either contained another IDU individual or a risk group that is other than an IDU or heterosexual, then the

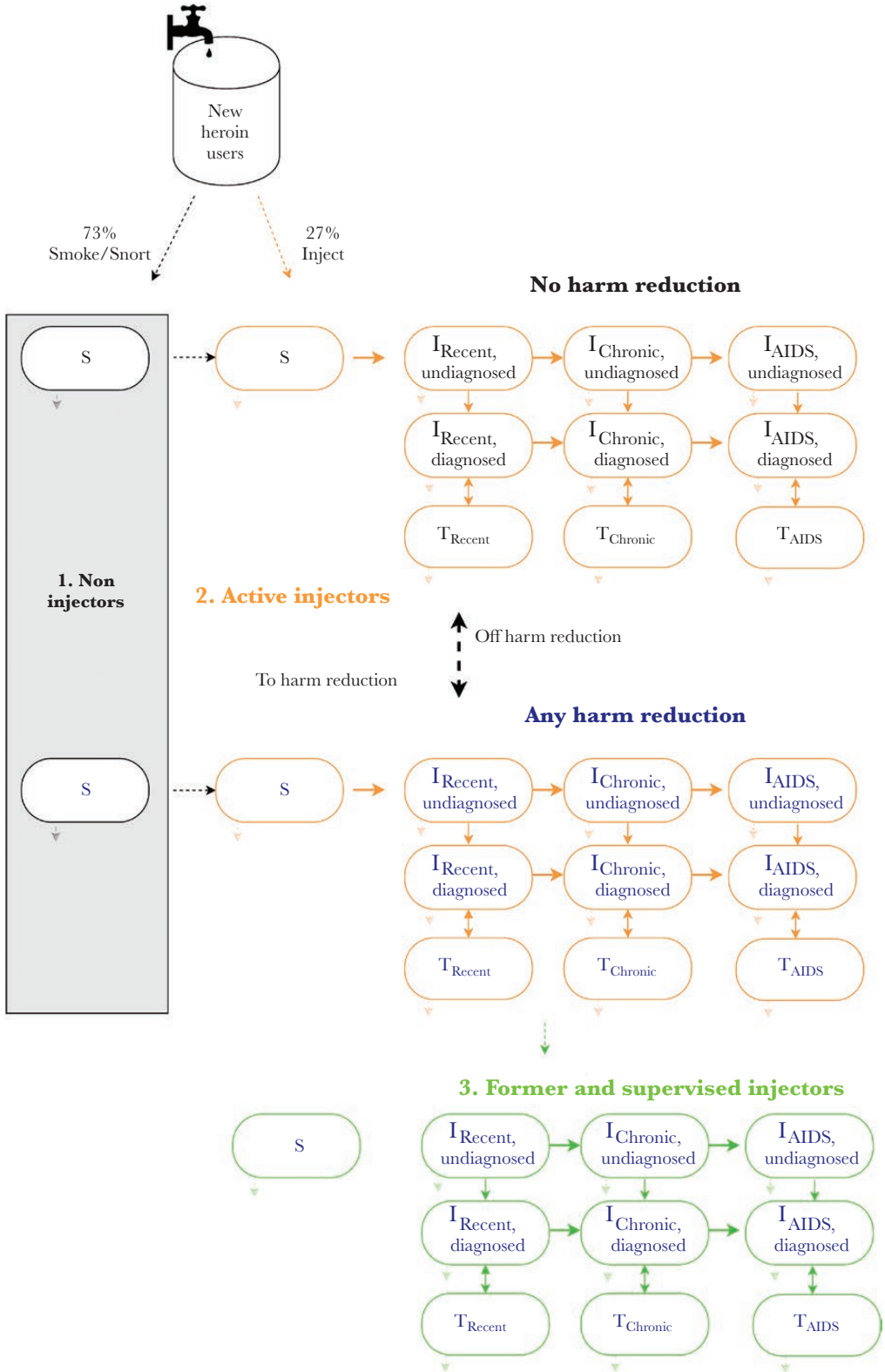

Figure 1. Graphical representation of the mathematical model. I, infected; S, susceptible; T, treated with cART (since 1996).

largest previous cluster was returned. This way, our analysis estimated not only the spillover population but also the further transmission of HIV within the heterosexual population caused by that spillover population. See the Supplementary Data for a detailed description of cluster analysis and the spillover calculation.

Analysis Tools

Statistical analysis was performed with R (version 3.2.3). The system of equations was solved using the package deSolve (version 1.14); the package "ape" (version 4.1) was used for phylogenetic analysis.

RESULTS

Injecting Drug Users in the Swiss HIV Cohort Study

Between 1983 and 2016, 4806 IDUs were enrolled in the SHCS, 3311 of those were most likely infected with HIV through sharing infected paraphernalia, and the remaining 1495 might have been infected via sharing or via sexual route.

The number of newly enrolled IDUs decreased with time from 553 newly registered in 1990, to 17 in 2016 (P for trend <.0001; Figure 2), hence accurately reflecting the drop of HIV incidence among IDUs in Switzerland [17]. Most IDUs were men (65.7%, 3157 of 4806; Supplementary Table 1) and were without university education (99.1%, 4761 of 4806). Both time to cART and subsequently the fraction of IDUs with AIDS-defining illness have decreased with time (P for trend .048), with almost immediate treatment initiation in 2010–2016, and 15.9% (11 of 69) of IDUs with AIDS-defining illness, compared with 48.0% (1441 of 2999) for IDUs that were diagnosed until 1990 (Fisher's exact test, $P < .0001$).

The period prevalence of HBV and HCV coinfections was high, with 78.3% (2312 of 2954; 1862 not tested) and 94.6% (2728 of 2883; 1923 not tested), respectively, for the entire period, and 58.2% (39 of 67; 2 not tested) and 73.1% (49 of 67; 2 not tested) in the last 7 years. This high prevalence of HBV and HCV alludes to a high fraction of nonassortative needle sharing, as expected in an open drug scene and assumed in our model.

Model Performance

The proposed model exhibits a qualitatively good fit, both to the annual number of newly diagnosed HIV cases among IDUs in Switzerland and to the annual number of reported AIDS deaths (Figure 3a and b, respectively). The model also catches, for the most part, the assumed dynamic of the population of problematic heroin users in Switzerland, with a peak during early 1990s and a subsequent gradual decline (Figure 3c). Finally, the model predicts HIV prevalence among IDUs in Switzerland, which falls in line with published estimates of approximately 10% between 1993 to 2000 [18]. Human immunodeficiency virus prevalence and the number of heroin users were deliberately not used for model fitting, to serve as an additional quality check for the prudence of our model; nevertheless, the dynamics of those compartments is captured well by the model.

The Combined Effect of Harm Reduction Measures, No Harm Reduction, and Sudden Discontinuation

First, we examined the extreme—yet relevant to other countries—worst-case scenario of no harm reduction at all since 1980, which required transferring the individuals on restricted methadone—that was available since late 1970s—to model compartments not covered by any harm reduction, from the start of the simulation. This resulted in 15 903 (range, 15 359–16 448) additional infections until the end of 2015 (Figure 4a and Figure 5), 5446 new additional AIDS deaths (range, 5142–5752) (Figure 4b), and a peak HIV prevalence of 50.7% (Figure 4c). Next, we examined whether a sudden discontinuation of all harm reduction services, after several years of low incidence, will result in a renewed outbreak. Our model shows that suddenly discontinuing all harm reduction in the year 2000

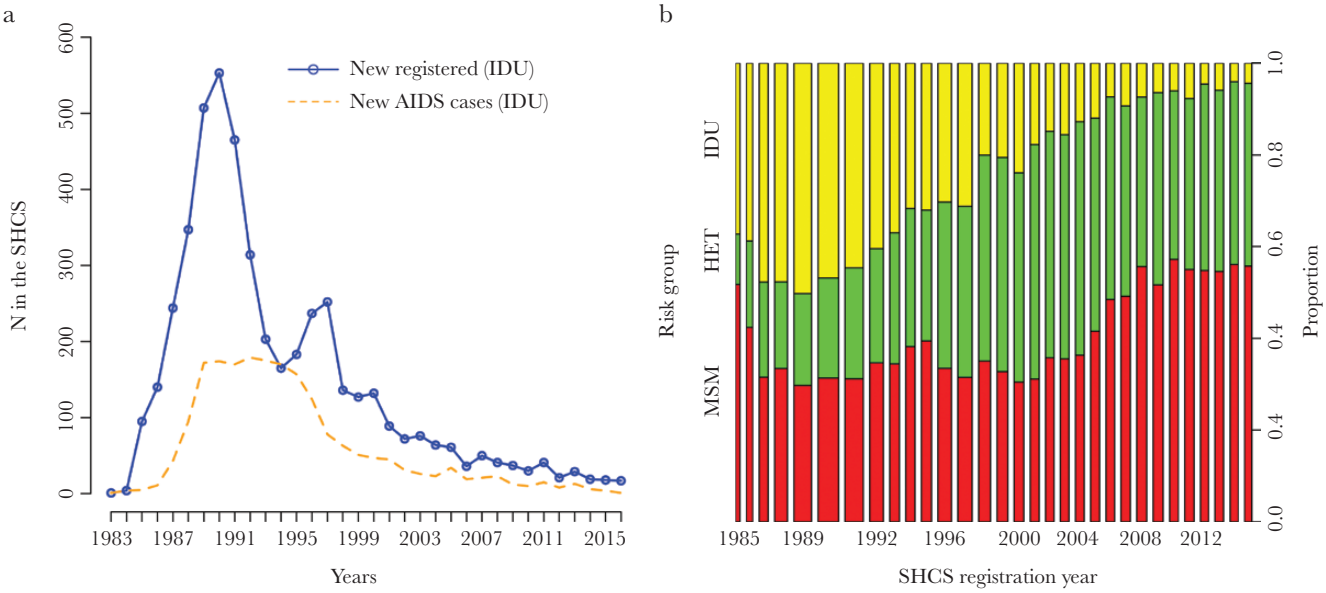

Figure 2. (a) New registered injecting drug users (IDUs) and new acquired immune deficiency syndrome (AIDS) cases in the Swiss HIV Cohort Study (SHCS). (b) The fraction of IDUs (yellow) out of all newly registered patients in the Swiss HIV Cohort Study, by registration year.

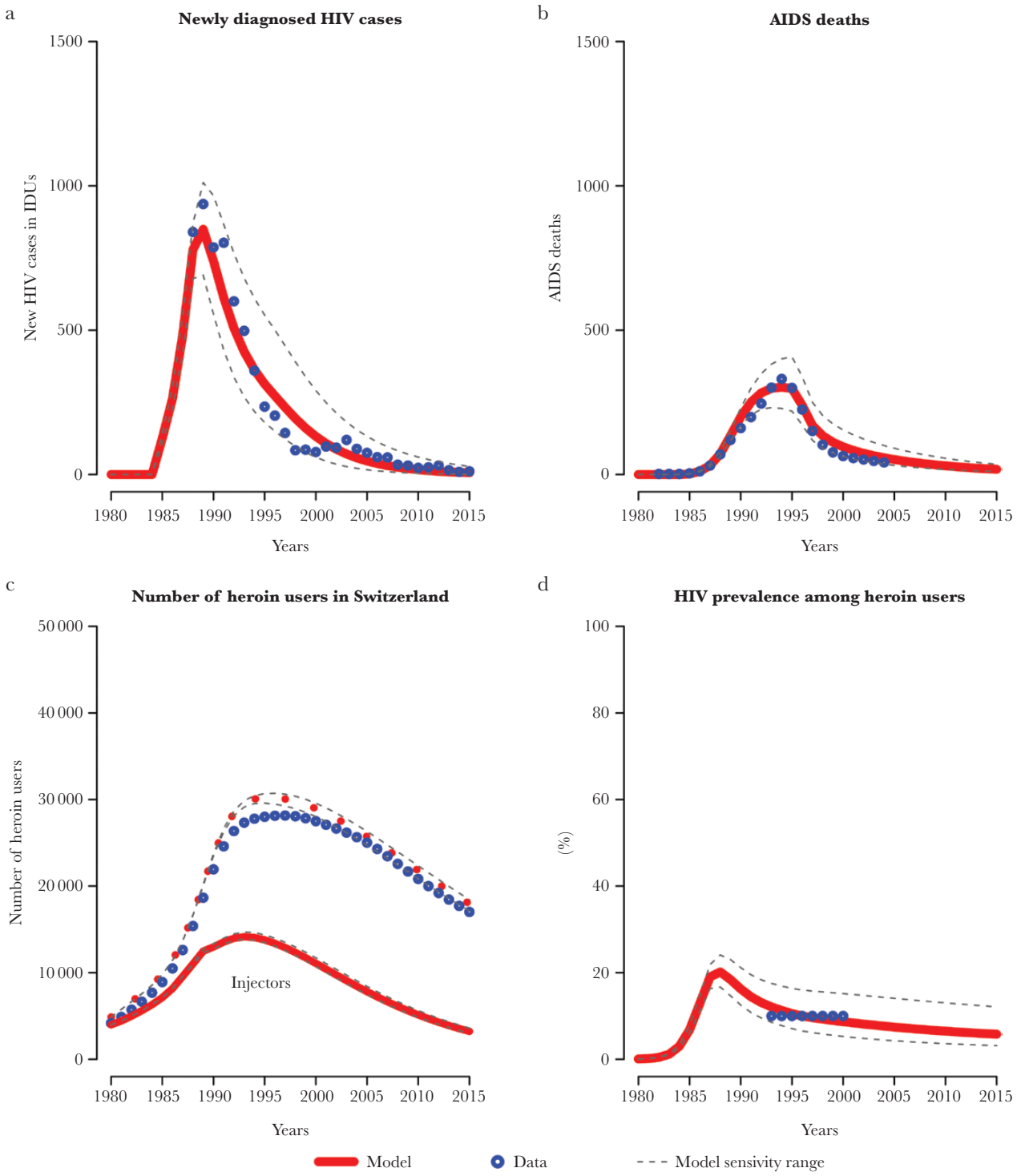

Figure 3. Model fit versus reported data. Source: (a) incidence [17, 20, 37], (b) acquired immune deficiency syndrome (AIDS) deaths [17], (c) number of heroin users [13] (extrapolated 2010–2015), (d) human immunodeficiency virus (HIV) prevalence [18].

(10 years after the incidence peak) or 2005 would have resulted in outbreak re-emergence up to 2015 in both scenarios, with 4965 (range, 3420–6511) and 1351 (range, 779–1925) additional HIV cases, respectively (Figure 4a and Figure 5). However, the re-emergence rate is twice as slow when harm reduction is discontinued in 2005 compared with 2000, with linear slopes of 20.2 (95% confidence interval [CI], 18.8–21.6) and 40.5 (95% CI, 39.6–41.3) new cases, respectively, for the first 5 years after discontinuation. Because of immediate cART in the recent years, discontinuation in 2005 would have had limited to no

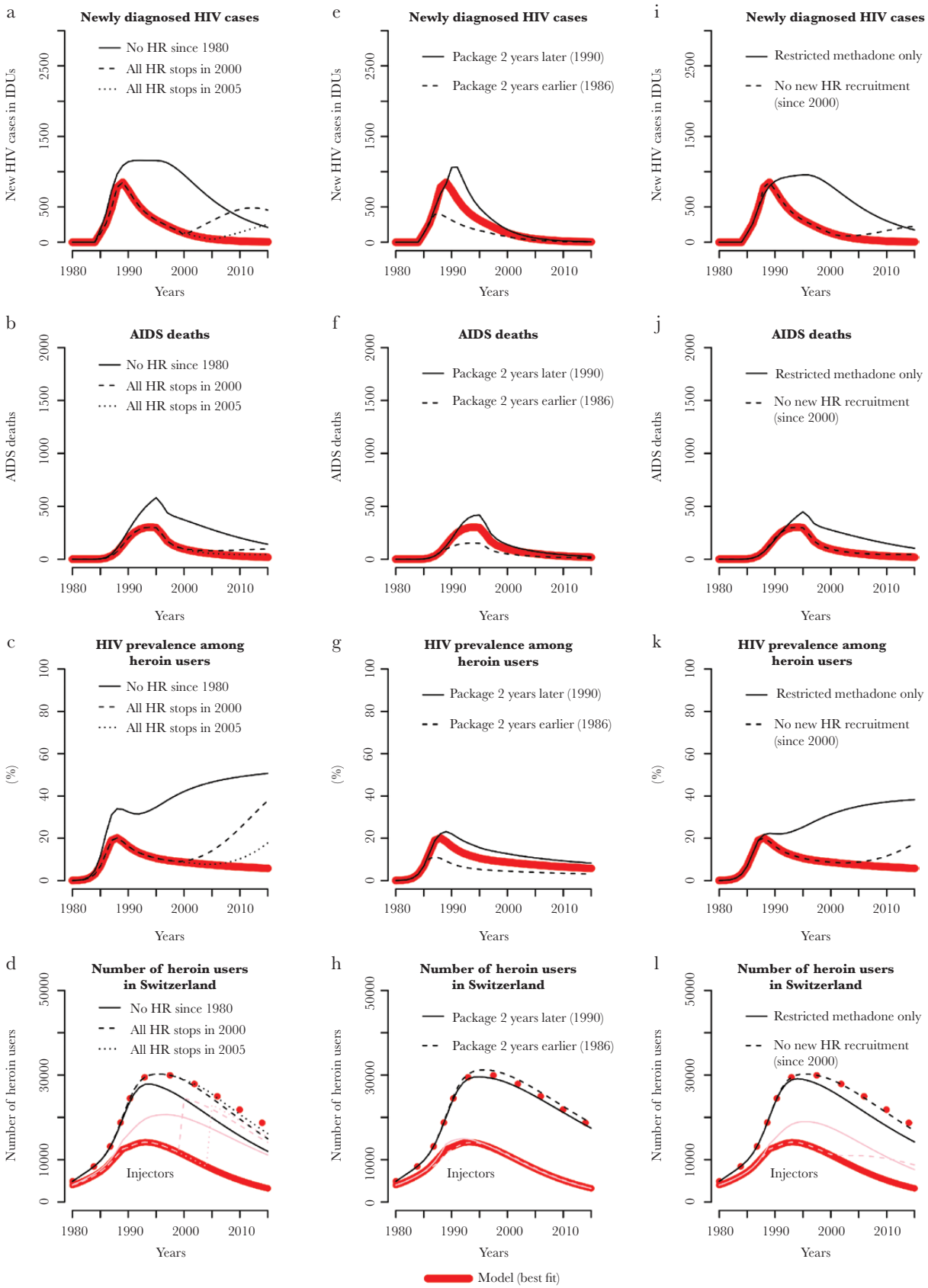

Figure 4. Seven counterfactual scenarios examined in this study. (Column 1, a–d) No harm reduction (HR) since 1980, All HR stops in 2000, All HR stops in 2005. (Column 2, e–h) HR package introduced 2 years later (1990), HR package introduced 2 years earlier (1986). (Column 3, i–l) Restricted Methadone only (entire period 1980–2015), no new HR recruitment since 2000.

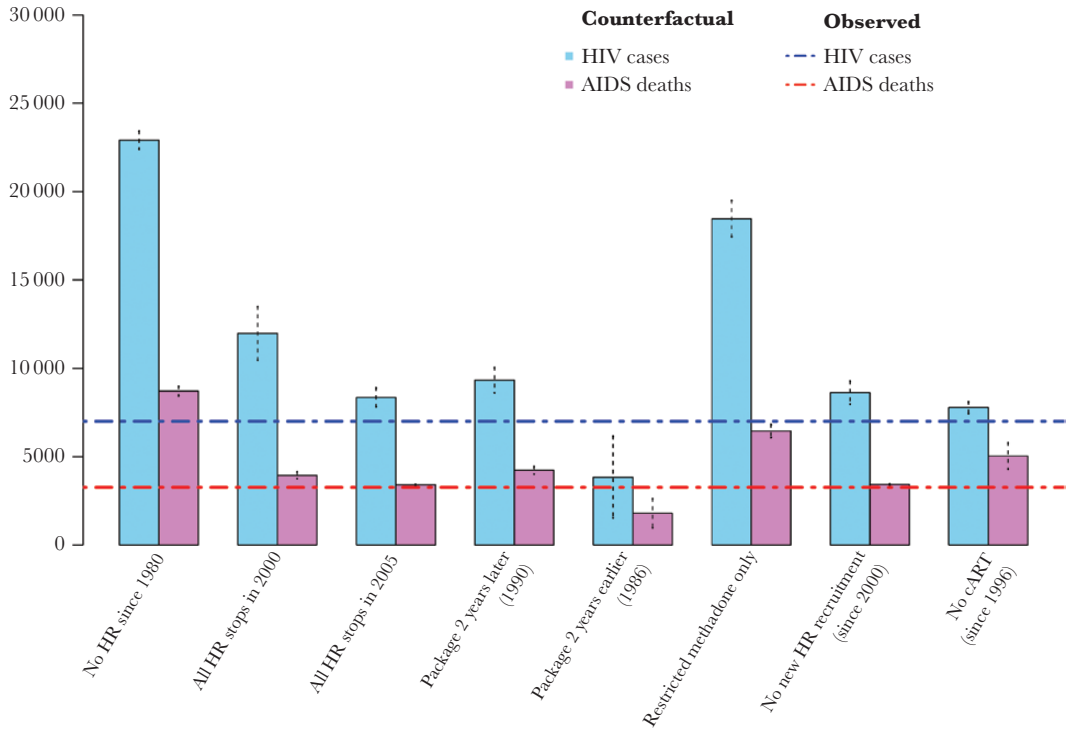

Figure 5. Total number of human immunodeficiency virus (HIV) cases and acquired immune deficiency syndrome (AIDS) deaths among injecting-drug-users in Switzerland, 1980–2015, across the examined scenarios and compared with the reported data (as model best fit). The no-combined antiretroviral treatment (cART) scenario is shown as well. Black dashed bars represent sensitivity analysis range. HR, harm reduction.

effect on the number of AIDS deaths with 153 (range, 101–206) additional deaths (Figure 4b).

Delayed or Earlier Introduction

A delay of 2 years in the introduction of the harm reduction package, ie, 1990 instead of 1988, would have resulted in 2325 (range, 1580–3071) additional HIV cases (Figure 4e and Figure 5) and 971 additional AIDS deaths (range, 724–1219) (Figure 4f). On the other hand, a 2 years earlier introduction (ie, 1986) could have halved the epidemic, preventing 3161 (range, 822–5499) HIV infections and 1468 (609–2326) AIDS deaths, with a peak HIV prevalence among IDUs that would have never exceeded 11.3 % (range, 8.5%–15.3%).

Only Restricted Methadone and No New Recruitment Since 2000

Next, we examined the effect of not introducing the extensive harm reduction package but continuing with high-threshold methadone only, with the same recruitment rate as before 1988 (~8.5% per year; Supplementary Data). This would have resulted in 11 462 additional HIV cases (range, 10 399–12 526) (Figure 4i and Figure 5) and 3190 (range, 2793–3588) additional AIDS deaths (Figure 4j). It is notable that restricted methadone is still superior to the scenario with no harm reduction at all, with 4441 prevented cases and 2256 fewer deaths. Finally, we explored a less radical discontinuation scenario, in which individuals that are covered by harm reduction remain in the covered compartment (with the same dropout rate); however, since 2000, there is no new recruitment to the harm reduction covered compartments. This scenario emulates a harm reduction budget cut plot. This would have resulted in a slow re-emergence with 1616 additional HIV cases (range, 938–2295) (Figure 4i) with no substantial increase in additional AIDS deaths (range, 114–235) (Figure 4j).

The Effect of Combined Antiretroviral Treatment

Although, chronologically, the epidemic reached its peak and began to decline before cART introduction in 1996, we still observe a moderate protective effect of cART (the harm reduction-related parameters were not changed in this scenario), with 771 (range, 401–1142) new HIV cases prevented by cART alone until the end of 2015, and—as expected—an ample effect on AIDS deaths, with 1771 (range, 991–2552) prevented deaths (Figure 5 and Supplementary Figure 3).

Spillover to the General Population

The phylogeny contained 4235 sequences from 2399 SHCS IDUs, with 94.3% (2262 of 2399) harboring subtype B. Cluster analysis showed 499 heterosexuals clustered with IDU in Swiss-only clusters, which were linked to 358 putative cross-risk-group introduction events (Supplementary Figure 4) in which the phylogenetically closest IDU was male in 60.3% (216 of 358) and female in 39.7% (142 of 358). In absence of any harm reduction (scenario a), the estimated additional number of heterosexuals whose infection originated from HIV-positive IDUs

is estimated to have been 2540 (range, 2453–2627) new infections, which is comparable to the total national HIV incidence among heterosexuals in the entire period from 2007 to 2015 (n = 2476, Federal Office of Public Health [19–21]).

DISCUSSION

According to UNAIDS, in Eastern Europe and Central Asia, 51% of all newly diagnosed HIV is attributed to people who inject drugs [22]. However, only 7% to 15% of all IDUs in Eastern Europe have access to needle and syringe programs, whereas for opioid substitution treatment the coverage is approximately 1% [3], and it remains illegal in Russia. Likewise, the Western-Europe, North-America, and Australasia region combined have not yet reached the WHO middle-coverage target of 20% for needle and syringe programs [7].

Our model estimates that a very high prevalence of HIV (~50%) among IDUs would have occurred in the absence of harm reduction. More importantly, our model takes into account both the overall decrease in heroin consumption as well as the decreasing number of injectors. Thus, the high prevalence in the absence of harm reduction is predicted to have occurred despite those general trends of drug use. This counterfactual estimate is also in line with historical seroprevalence data from socioeconomically comparable areas that had little to no harm reduction at that time. Frankfurt, Germany, had a large open drug scene, with HIV prevalence of 73.7% in 1994 [23], in Spain the prevalence was 63% in 1996 [24], and in northern Italy the prevalence was 49% in 1989 [25]. Some areas in the United States also exhibited high HIV prevalence, with 61% in New York [26] and 60% in New Haven, Connecticut [27], during the early 1990s. In Eastern Europe, and especially in Russia, which exercises a repressive approach toward IDUs and repulsion of the harm reduction concept on the political level, a 37% prevalence was estimated in 2003 [3]. In Estonia, the rate was as high as 72% [3].

Considering the low incidence of HIV among IDUs in Switzerland in the recent years, there is a growing debate on whether the funds invested in harm reduction can be safely allocated elsewhere. In 2016, the canton of Zürich decided to cut 4.5 million Swiss Francs from the drug-addiction treatment programs until 2019 [28]. Our study shows that suddenly stopping harm reduction measures, even several years after the epidemic appears as under control, can lead to a new outbreak. This result is supported by a recent experience from Greece, a country with a historically low HIV incidence among IDUs (1.5% to 4.5% of all new infections during 2000–2010) [29]. In 2011, due to the fiscal crisis and severe austerity, the harm reduction measures were underperforming [30]. Until the first 8 months of 2013, 1000 new HIV cases among IDUs have already been diagnosed [31]. After harm reduction—in form of needle and syringe exchange and opioid-substitution—was scaled up again, HIV incidence was reduced 5-fold within 1 year [32].

Our estimates show a moderate impact of cART on curbing HIV transmission among IDU in Switzerland. This can be attributed to 2 factors: (1) cART was introduced in 1996 after the epidemic was already contained by the harm reduction measures, which started in part in 1988; and (2) the effect of cART is partly undermined by lower adherence among IDUs [33], which was also reflected in our model. However, as expected, cART prevented a large number of AIDS deaths among IDUs.

Our model has several benefits and can be adjusted for the following factors: (1) the decrease in the number of injectors with time; (2) the possible reduction in risk behavior even in people who are not reached by any harm reduction due to overall awareness of HIV [34]; and (3) the decrease in needle sharing by IDUs who are aware of their HIV-seropositive status and are concerned of infecting others [35]. Because the extent of the relevance of those developments to the Swiss settings is uncertain, we speculate that we might have underestimated the effectiveness of the combined harm reduction measures and that our estimates lay on the conservative side. This is further supported by the fact that, due to scarcity of data, we could not account for cocaine-only injectors; however, injectors of cocaine and heroin ("Speedball") were accounted for in our model. In addition, our model has the advantage of being applicable to the current opioid analgesics-driven HIV epidemic, because it accounts for the transition from a noninjecting to injecting drug administration mode.

Our model is limited because it does not differentiate between the different measures implemented, except for restricted methadone. However, in this work, we were a priori interested in cumulative estimates. Our model also only accounts for sexual transmission within but not between the 3 meta-strata. Nonetheless, the contribution of sexual transmission is expected to be of secondary importance due to an 8-fold higher per-act transmission probability for needle sharing [36]. Finally, as it is often in modeling studies, the uncertainty ranges of our predictions might be underestimated.

Indeed, not all countries affected by an HIV epidemic among IDUs possess the resources that were available in Switzerland. However, the unit costs of harm reduction interventions are relatively low and are estimated to be highly cost effective [7] and, in light of the results presented here, might even be cost saving. In addition, we demonstrated that the benefits of harm reduction extend beyond the population of IDUs, with thousands of averted spillover heterosexual infections. Similar studies are needed for the HCV epidemic, which affects this population even more severely than HIV.

CONCLUSIONS

In summary, our results highlight, based on the Swiss experience, the pivotal role of harm reduction for successful curbing of HIV transmission among IDUs and prevention of grave repercussions for the general population.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Members of the Swiss HIV Cohort Study. Anagnostopoulos A., Battegay M., Bernasconi E., Böni J., Braun D. L., Bucher H. C., Calmy A., Cavassini M., Ciuffi A., Dollenmaier G., Egger M., Elzi L., Fehr J., Fellay J., Furrer H. (Chairman of the Clinical and Laboratory Committee), Fux C. A., Günthard H. F. (President of the SHCS), Haerry D. (Deputy of "Positive Council"), Hasse B., Hirsch H .H., Hoffmann M., Hösli I., Huber M., Kahlert C., Kaiser L., Keiser O., Klimkait T., Kouyos R. D., Kovari H., Ledergerber B., Martinetti G., Martinez de Tejada B., Marzolini C., Metzner K. J., Müller N., Nicca D., Paioni P., Pantaleo G., Perreau M., Rauch A. (Chairman of the Scientific Board), Rudin C. (Chairman of the Mother & Child Substudy), Scherrer A. U. (Head of Data Centre), Schmid P., Speck R., Stöckle M., Tarr P., Trkola A., Vernazza P., Wandeler G., Weber R., Yerly S.

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