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Review

Association of opioid agonist therapy with the initiation of antiretroviral therapy - a systematic review

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ABSTRACT

Objectives: People who inject drugs are at high risk of HIV infection but often face barriers in accessing medical care including access to antiretroviral therapy (ART). Evidence is available about the effectiveness of opioid agonist therapy on drug dependency and risk behaviors. However, it remains scattered regarding access to ART among HIV-positive people who inject drugs. We conducted a systematic review to examine the association of opioid agonist therapy with ART initiation among HIV-positive people who inject drugs.

Methods: We searched the literature for evidence from seven databases. We conducted a narrative synthesis and meta-analysis to examine the association of opioid agonist therapy with ART initiation.

Results: Five out of 2,901 identified studies met the inclusion criteria. Three out of five studies reported that, HIV-positive people receiving opioid agonist therapy initiated ART more than those not receiving opioid agonist therapy. In meta-analysis, opioid agonist therapy was associated with ART initiation among HIV positive people who inject drugs (pooled odds ratio: 1.68; 95% confidence interval: 1.03–2.73).

Conclusions: Opioid agonist therapy is positively associated with ART initiation among HIV-positive people who inject drugs. It is important to scale up opioid agonist therapy among people who inject drugs to improve their ART initiation.

1. Introduction

People who inject drugs are at high risk of contracting human immunodeficiency virus (HIV) infection, owing to their high-risk injecting,[1] and sexual behaviors.[2] About 1.7 out of 12.2 million people who injected drugs were infected with HIV in 2013.[3] This population is recognized as a point source of HIV infection for the general populations, both in concentrated and generalized epidemics. They may engage in high-risk sexual behaviors with their injecting or non-injecting drug use partners. Unrestricted access of HIV care by people who inject drugs is necessary to control the HIV epidemic.

Many people who inject drugs do not have access to antiretroviral therapy (ART) despite their need. ART improves morbidity and mortality[4,5] and prolongs lives of HIV-positive individuals. ART may also decrease the transmission of HIV infection.[6–8] Only four out of 100 HIV-positive people who inject drugs receive ART in 47 countries where reports of ART use were available among people who inject drugs.[9] People who inject drugs face various barriers to access ART and other health care services. People who use drugs do not often trust the health care system and expect that they will be treated punitively.[10] They sometimes perceive discrimination and fear of negative reactions from health workers.[11] In addition, people who use drugs may be denied treatment due to co-morbidity of medical conditions[12,13] and medical practitioners' fear of inadequate compliance to treatment, once initiated.[12,14]

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Treatment of opioid dependence may improve access to ART among people who inject drugs.[15,16] Medications for opioid dependence can either be agonists such as methadone or partial agonists such as buprenorphine or antagonists such as naloxone.[17] However, provision of opioid agonist therapy to people who inject drugs is still low. For instance, less than 2% of people who inject drugs are provided with opioid agonist therapy in each of the following five countries: China, Malaysia, Russia, Ukraine and Vietnam. Almost half of all HIV-positive people who inject drugs live in these five countries.[18] In an opioid agonist therapy program, people who inject drugs receive medications to treat opioid dependence.[19]

Opioid agonist therapy programs may be linked to medical services. This allows provision of medical care at the harm reduction sites[20,21] Additionally, people who inject drugs may be referred to nearby medical clinics or specialized care facilities when in need.[22] Such medical care may include primary medical care, ART, and hepatitis treatment services. In addition, opioid agonist therapy improves physical and social functioning of clients.[23,24] These provisions are more likely to help people who inject drugs achieve physical and social stabilization and overcome barriers of access to ART. Although such evidence is available, no systematic review has been conducted to examine the association of opioid agonist therapy with ART initiation among HIV-positive people who inject drugs. Therefore, we conducted this systematic review to examine the association of opioid agonist therapy with ART initiation among HIV-positive people who inject drugs. The results of this review will assist policy makers in making decisions about the problem of low ART coverage among people who inject drugs.

2. Methods

This systematic review aimed to answer the following population, intervention, comparator, and outcome (PICO) question: "What is the association of opioid agonist therapy with ART initiation among people who inject drugs who are on opioid agonist therapy compared to those who are not on such therapy?" In this review, we defined the population as people who use illicit drugs by means of injection and are living with HIV regardless of their age. The intervention was being on opioid agonist therapy. In such interventions, clients receive medications such as buprenorphine and methadone for treating opioid dependence.[19,25] The comparison group consisted of people who use illicit drugs by means of injection and are living with HIV but are not on opioid agonist therapy. The outcome of interest was ART initiation.

We excluded studies which included people who inject drugs enrolled in detoxification centers from our review. These centers are used to minimize withdrawal symptoms of addicted clients in a safe and effective manner. We excluded these studies because, detoxification processes in such centers may or may not involve the use of medications such as methadone and buprenorphine.[26]

We first developed a protocol and registered it at the PROSPERO database for systematic reviews (Supplementary file 1). The registration number of the protocol is CRD42014009118.[27] In this registered protocol, the primary outcome variables were access to general medical care and the initiation of treatment for HIV and hepatitis. However, in the current study, we have reviewed and reported the results on the outcome of the initiation of HIV treatment only.

2.1. Data sources for existing reviews

Two reviewers (LBM and BFS) independently searched for the presence of systematic reviews or protocols similar to the one used for this review. This search was conducted in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Campbell Library of Systematic Reviews, and the National Institute for Health and Care Excellence. No similar review was found.

2.2. Evidence search strategy

We used sets of prepared Boolean phrases and search terms to retrieve evidence from various medical and academic databases. Similarly, the two reviewers (LBM and BFS) independently conducted a literature search in PubMed, the Education Resources Information Center, PsycINFO, the European Monitoring Centre for Drugs and Drug Addiction, the National Institute on Drug Abuse, the United Nations Office on Drugs and Crime, and World Health Organization databases. For the PubMed database, we used a Boolean combination search term (Supplementary file 2). We used similar text words to conduct searches in the other databases. We also conducted a hand search from references of journal articles that we retrieved. The last search for this review was conducted on 1st November 2014. The searches for various databases were conducted within three months. We limited our screening to studies which were reported in English language. No limit was set for the dates of publication of the articles. The two reviewers compared their results for each database, resolved minor differences and reached a final article inclusion list. We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary file 3) and used the PRISMA flow diagram to retrieve and report the evidence (Figure 1).[28]

2.3. Inclusion and exclusion criteria

We included studies of prospective cohort design with control groups or those comparing an outcome before and after the intervention. We also included cross-sectional studies with control groups. We also searched for randomized controlled trials however none was found which addressed our PICO question. We excluded qualitative studies, reviews, case reports, or editorials.

2.4. Data extraction

The two researchers (LBM and BFS) independently extracted data. The differences were resolved by consensus. We conducted data extraction using an excel spreadsheet. It contained the following elements: study author, year of publication, country in which the study was conducted, study design, intervention characteristics including the medications used for opioid agonist/antagonist therapy and length of follow-up of the intervention, participants of the study, and results of the study.

2.5. Data synthesis and analysis

Five studies were included in this review.[29–33] A narrative synthesis was described for all five studies and a meta-analysis was conducted for four studies[29,30,32,33] for the outcome of ART initiation (Figure 1). A fifth study[31] was not included in the meta-analysis because it had no control group.

For meta-analysis, we calculated the odds ratio (OR) and 95% Confidence Interval (CI) using the Mantel-Haenszel analysis in a random-effect model. We assessed heterogeneity of studies using Chi-square (χ^2) and I^2 statistics. The I^2 statistic describes the percentage of variation in the observed estimates of effect from the included studies due to heterogeneity rather than chance. We used an alpha level of 0.05 for meta-analysis, except for testing heterogeneity, where we used $p < 0.10$. We used Review Manager 5.3[34] to conduct meta-analysis.

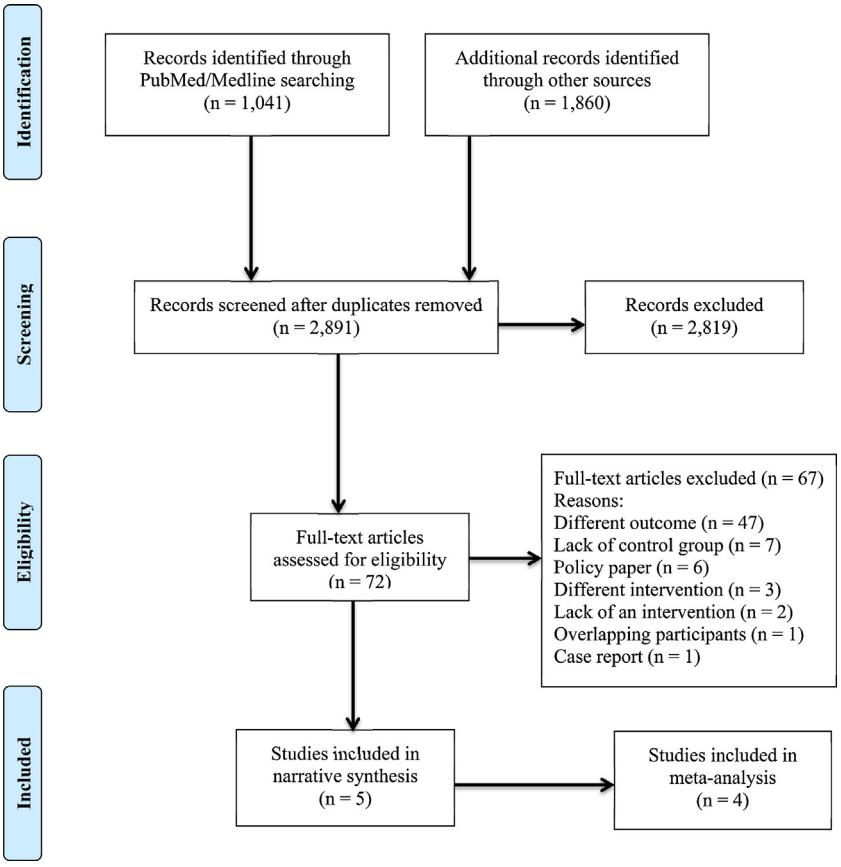

Figure 1. PRISMA Flow diagram to show the systematic review process (PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

3. Results

3.1. Systematic review process

Figure 1 shows the results of the review process. We identified 2,901 articles from our database searches. Of them, we identified 1,041 articles from PubMed and 1,860 articles from other databases and hand search. After excluding duplicates, we screened 2,891 articles based on titles and abstracts, and retrieved 72 articles for full text review. We excluded 67 articles for various reasons including different outcome (n = 47), lack of a control groups (n = 7), policy papers (n = 6), different interventions (n = 3), lack of an interventions (n = 2), overlapping participants (n = 1) and a case report (n = 1). Five studies were included in this review.[29–33]

3.2. Description of included studies

Of five included studies, two were conducted in the USA[31,32] and others in Switzerland,[29] Canada[30] and Ukraine.[33] Regarding the study design, three were prospective cohort studies[29–31] and two were cross-sectional studies.[32,33] For opioid agonist therapy, people who inject drugs received methadone, buprenorphine, naloxone, or legal heroin (Table 1).

3.3. Study quality assessment

The two researchers (LBM and BFS) independently conducted study quality assessment. We assessed risk of bias, using a Risk of Bias Assessment for Non-randomized Studies tool for observational studies.[35] We assessed six types of risk of biases: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. All five included studies had an unclear risk of bias for blinding of outcome assessments and three studies had an unclear risk of bias for incomplete outcome data assessment[30,31,33] (Table 2).

We conducted grading of evidence for four studies[29,30,32,33] included in the meta-analysis. We evaluated these studies using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) technique.[36] The quality of studies was very low, and inconsistency was substantial however the risk of bias, indirectness and imprecision were not serious (Table 3). The quality of the studies was very low because of the observational type of the study designs of included studies, which are rated low quality and substantial heterogeneity observed in the meta-analysis of the included studies. We used the online Guideline Development Tool[37] to prepare the GRADE table.

3.4. Association of opioid agonist therapy with ART initiation

Table 4 shows a narrative synthesis of all five studies included in this review. A prospective cohort study conducted in Canada, reported a higher rate of ART initiation among participants on opioid agonist therapy (methadone) compared to those who were not on such therapy (64.2% vs. 44.8%; log-rank $p = 0.004$).[30] Another prospective cohort study without a control group conducted in the USA showed that, compared to baseline, participants who were on suboxone (buprenorphine/naloxone) were more likely to receive ART as the study observation time increased ($p < 0.05$).[31] Furthermore, the proportion of HIV-positive people who inject drugs who initiated ART was higher among participants on opioid agonist therapy (methadone) compared to that among participants not on such therapy in a cross-sectional study in the USA (88.1% vs. 33.8%; $p = 0.001$).[32]

Table 1
Description of included studies

Author	Country	Study design	Intervention drug	Intervention/study characteristics	Length of the OT study
Weber 2009[29]	Switzerland	Prospective cohort	Methadone/ buprenorphine/ legal heroin	The Swiss HIV Cohort Study (SHCS) consists of HIV positive individuals treated at HIV outpatient clinics and district hospitals. Opioid agonist therapy (OT) is not carried out by the SHCS centers but by specialized institutions or private physicians. ART initiation data were obtained through self-report.	10 years
Uhlmann 2010[30]	Canada	Prospective cohort	Methadone	The prospective cohort consists of HIV-positive PWID who complete a questionnaire at baseline and semi-annually. ART initiation data were obtained through self-report which was supported by a centralized province-wide ART dispensation program and a confidential record linkage.	8 years
Altice 2011[31]	USA	Prospective cohort	Buprenorphine/ Naloxone	Participants were from HIV clinical sites that provide integrated HIV primary care and buprenorphine/ naloxone treatment for opioid dependence. ART initiation data were obtained through self-report and confirmed by chart review.	12 months
Sambamoorthi 2000[32]	USA	Cross-sectional	Methadone	Participants were PWID who had AIDS. Data were retrieved from databases namely AIDS Registry, Medicaid paid claims and AIDS Community Care Alternatives Program. ART initiation data were obtained from pharmacy data.	8 years
Bachireddy 2014[33]	Ukraine	Cross-sectional	Buprenorphine/ methadone	The intervention group consisted of participants from Integrated/co-located clinic (ICL) or non-co-located clinic (NCL) while the control group consisted of participants from harm reduction and outreach (HRO) sites. ICL clinics provide treatment and screening for tuberculosis, HIV and opioid dependence using OT. NCL provide opioid dependence treatment using OT with substance abuse treatment counseling. HRO sites provide case management, referral for services such as HIV and tuberculosis, syringe exchange and psychosocial counseling. ART initiation data were obtained through self-report.	Participants in the intervention group had been enrolled > 3 months. Those in the control group (HRO) did not require to register

HIV, human immunodeficiency virus; PWID, people who inject drugs; AIDS, acquired immunodeficiency syndrome; OT, opioid agonist therapy

Table 2
Assessment of risk of bias for non-randomized observational studies

Author	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Weber 2009[29]	+	+	+	?	+	+
Uhlmann 2010[30]	+	+	+	?	?	+
Altice 2011[31]	+	+	+	?	?	+
Sambamoorthi 2000[32]	+	+	+	?	+	+
Bachireddy 2014[33]	+	+	+	?	?	+

+ Indicates low risk of bias ? Indicates unclear risk of bias.

Table 3
GRADE profile of 4 studies included in the meta-analysis

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No OT	OT	Relative (95% CI)	Absolute (95% CI)	
4[a]	Observational studies	Not serious	Serious	Not serious	Not serious	None	748/1245 (60.1%)	388/1047 (37.1%)	OR 1.68 (1.03 to 2.73)	116 more per 1000 (from 7 more to 203 more)	⊕○○○ Very low

GRADE, Grades of Recommendation, Assessment, Development and Evaluation; OT, opioid agonist therapy.
[a] Studies:[29,30,32,33]

On the other hand, the difference in proportion of ART initiation between participants on opioid agonist therapy (methadone/buprenorphine/legal heroin) and those not on such therapy in a prospective cohort study in Switzerland was not statistically significant (20.1% vs. 20.6; p = 0.9).[29] Also, the difference in proportion of ART initiation between participants on opioid agonist therapy (buprenorphine/methadone) and those not on such therapy in a cross-sectional study in Ukraine was not statistically significant (33.8% vs. 26.3%; p = 0.19).[33]

Meta-analysis of the four studies showed that opioid agonist therapy is positively associated with ART initiation among people who inject drugs (pooled OR: 1.68; 95% CI: 1.03-2.73). However, heterogeneity may be substantial ($\chi^2 = 10.61$; $I^2 = 72\%$; p = 0.01) (Figure 2).

4. Discussion

In this systematic review, opioid agonist therapy is positively associated with ART initiation among HIV-positive people who inject drugs. Individuals with opioid dependence are more likely to be mentally, physically, and socially disadvantaged especially when they have been on opioids for a long time.[38,39] Treatment with opioid agonist therapy has been shown to improve physical and social functioning for these individuals.[23,24] People who inject drugs on opioid agonist therapy are more likely to achieve physical and social stabilization, and as a result, they are more likely to overcome the barriers associated with access to medical care and improve their ART initiation.

Of five studies, three reported that, HIV-positive people receiving opioid agonist therapy initiated ART more than those not receiving opioid agonist therapy. Barriers of access to health care might have contributed to the lack of benefit of opioid agonist therapy on ART initiation in the two studies conducted in Switzerland[29] and Ukraine.[33] In Switzerland, ART could be easily accessed therefore the individual factors might have played a major factor. More individuals were actively injecting drugs in the intervention group than in the control group in the study conducted in Switzerland.[29] Active injecting drug use might have influenced them to prioritize drug use than focusing on their personal health.[40]

Table 4
Association of opioid agonist therapy on ART initiation - a narrative synthesis

Author	Country	Study design	Total sample	HIV disease severity	Results
Weber 2009[29]	Switzerland	Prospective cohort study with a control group	748 participants (607 on OT, 141 not on OT)	At baseline, median (IQR) nadir CD4 cell count was 245 (120–470) in the OT group and 277 (156–512) cells/μL in the non-OT group; 17.3% and 9.2% had AIDS in the OT and non-OT groups respectively	Between baseline and last visit, there was no a statistically significant difference in initiating ART between participants on OT and those not on OT (20.1% vs. 20.6; p = 0.9).
Uhlmann 2010[30]	Canada	Prospective cohort study with a control group	231 participants (55 on OT, 176 not on OT)	At baseline, viral load (≥ 100,000 copies/mL) in the OT and non-OT: 24% vs. 33%, p = 0.237; CD4 count (< 200 cells/mm^3): 16% vs. 22%, p = 0.312.	24 months after recruitment, the rate of ART initiation was higher among participants on OT than those not on OT (64.2% vs. 44.8%; log-rank p = 0.004).
Altice 2011[31]	USA	Prospective cohort: pre-post intervention study	295 at baseline, 187 at follow-up (All participants on OT, no control group)	At baseline, mean CD4 count, 354.9 cells/mL (261 participants).	At baseline, 59.7% of participants were on ART and at follow-up 68.4% of participants were on ART. Compared with baseline, participants were more likely to receive ART as the observation time increased (p < 0.05).
Sambamoorthi 2000[32]	USA	Cross-sectional study with a control group	1017 participants (184 on OT, 833 not on OT)	All participants had AIDS.	The proportion of ART initiation was higher among participants on OT than those not on OT (88.1% vs. 73.8%; p < 0.001).
Bachireddy 2014[33]	Ukraine	Cross-sectional study with a control group	296 participants (201 on OT, 95 not on OT)	CD4 monitoring in the past 6 months: 87.6% in the OT and 64.8% in the non-OT group.	The proportion of ART initiation was not statistically significant among participants on OT compared to those not on OT (33.8% vs. 26.3%; p = 0.19).

OT, opioid agonist therapy; ART, antiretroviral therapy; IQR, interquartile range.

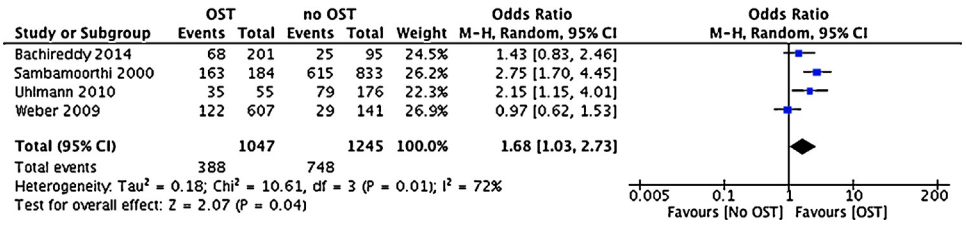

Figure 2. Effectiveness of OST on the initiation of ART among people who inject drugs–meta-analysis (OST, opioid substitution therapy; ART, antiretroviral therapy).

The results of this systematic review are supported by the following studies, although they did not meet the inclusion criteria for this review. One of them is a cross-sectional study in Ireland where receiving ART was positively associated with being on methadone maintenance treatment among people who inject drugs.[15] In another study in Ukraine, a total of 207 people who use drugs were enrolled in the national buprenorphine maintenance treatment program nine months after it had started. Of them, 55% were HIV-positive and 25% had started ART.[41] Moreover, in a cohort study in Indonesia among 223 people who inject drugs enrolled in the study, the methadone clinic was responsible for diagnosing 31.9% of HIV-positive participants and initiating ART for 45.7% of the participants.[16] Lastly, ART use was positively associated with use of methadone maintenance treatment among people who inject drugs in cohort studies in Canada.[24,42]

This study has several limitations. First, the included studies were observational (cohort studies, cross-sectional studies and a pre-post interventional study with no control group). In these studies unmeasured motivational and related factors might have led people who inject drugs engaging in opioid agonist therapy to also be more diligent in seeking ART. To control for the differences of the included studies, a risk of bias assessment was conducted for all five included studies, and graded the quality of evidence for four of studies included in the meta-analysis. Second, in meta-analysis, heterogeneity might be substantial. Substantial heterogeneity might be due to the differences in duration of follow-up of the interventions of the included studies that ranged from three months to thirteen years. Third, most of the studies were from developed countries and only one study was from a developing country. Therefore, it may not be possible to generalize these results to all countries with the problem of injection drug use. Despite these limitations, this is the first systematic review that examined the association of opioid agonist therapy with ART initiation among HIV-positive people who inject drugs.

5. Conclusions

Five studies were included in this systematic review. Three of them reported that HIV-positive people receiving opioid agonist therapy, initiated ART more than those not receiving opioid agonist therapy. The overall effect size through meta-analysis shows that opioid agonist therapy is positively associated with ART initiation among HIV-positive people who inject drugs. However, these results should be interpreted with caution due to substantial heterogeneity observed among the included studies.

For people who inject drugs, their improved access to opioid agonist therapy and ART is crucial. To improve ART initiation among them, opioid agonist therapy should be scaled up. When they are on opioid agonist therapy, they can receive ART at the opioid agonist therapy site. Also, they can be referred to off-site HIV care and treatment centers and then still initiate ART.[43] However, people who inject drugs face many barriers in accessing health care including lack of transport. Therefore, these barriers should be considered while establishing opioid agonist therapy programs which provide medications for opioid dependence only without HIV care and treatment at the same site. Furthermore, it is important to conduct more assessments to examine the association between opioid agonist therapy and ART initiation using cohort study designs or cross-sectional studies with control groups as only five studies were included in this systematic review.

Contributions: LBM conceived and designed the study, searched the literature, analyzed the data and drafted the manuscript. BFS designed the study, searched the literature and critically reviewed the study. JKKM critically reviewed the manuscript. OSU critically reviewed the manuscript. JY critically reviewed the manuscript. MJ designed the study and critically reviewed the manuscript.

Conflicts of interests: None of the authors have conflicts of interests to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2016.03.022.

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