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Assessing the Potential Impact of a Kidney Exchange Program in Mexico

Short running title: Potential Impact of a KEP in Mexico

Keywords: Kidney disease, Kidney exchange program, Simulation, Optimization

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Abstract Page

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List of abbreviations for the article

CENATRA, Centro Nacional de Trasplantes
DKP, Dutch Kidney Program
ESRD, End-Stage Renal Disease
HLA, Human Leukocyte Antigen
KEP, Kidney Exchange Program
LDKT, Living Donor Kidney Transplantation
NKR, National Kidney Registry
OPTN, Organ Procurement and Transplantation Network
PDP, Patient-Donor Pair
PRA, Panel-Reactive Antibody
UNOS, United Network for Organ Sharing
pmp, per million population
WL, Waiting List

Abstract

Introduction: In Mexico, more than 15,000 patients are waiting for a kidney transplant, and there are not enough kidneys from deceased donors to transplant them. A kidney exchange program could increase kidney transplants from living donors by matching altruistic living donors and biologically incompatible donor-recipient pairs. Several countries have implemented successful kidney exchange programs. We evaluated the impact of implementing a kidney exchange program in Mexico.
Methods: We simulated kidney exchange in Mexico using data from Mexican population distributions. We used an optimization model to maximize the number of compatible patient-donor matchings. Three different scenarios were evaluated.
Results: We estimated that almost 45% of patients on the waiting list have an incompatible donor, and 995 transplant candidates who have a living donor available are added to the waiting list annually. If a kidney exchange program were established in Mexico, the number of living-donor transplants could increase by up to 20%.
Conclusions: Implementing kidney exchange in the country may reduce the increase in the number of recipients on the waiting list and reduce costs in the long term. To succeed, the program must not only draw sufficient participation from incompatible pairs, but also ensure that these pairs remain in the program even if they have to wait to be matched.

Keywords. Kidney disease, Kidney exchange program, Simulation, Optimization

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1 Introduction

Many patients who need a kidney transplant can identify a living donor. A Living Donor Kidney Transplantation (LDKT) is considered the best treatment choice for patients with end-stage renal disease (ESRD) as it provides greater long-term survival rates and a better quality of life. LDKT can include preoperative desensitization in case of ABO blood type or human leukocyte antigen (HLA) incompatibility [1]. However, LDKT requires finding a compatible donor. When a patient's intended living donor, who is commonly a relative of the recipient, is not compatible with their patient, a kidney exchange transplantation can be an alternative.

A Kidney Exchange Program (KEP) has been implemented in several countries to match incompatible donor-recipient pairs for a kidney exchange transplantation [2]. Although KEPs have provided successful results in different countries, in Mexico there is no such a program at a national level, though a few kidney exchanges have been performed in Mexico. In this work, we analyze the impact of implementing a KEP in Mexico with a simulation using blood type distributions obtained from the Mexican population.

1.1 Kidney transplantation in Mexico

In Mexico, the first organ transplant was performed in 1963 with no pre-existing legislation. The first regulation was created in the Código Sanitario de los Estados Unidos Mexicanos in 1973. Since then, several laws, modifications, and collaborations have been carried out to improve and regulate the organ transplantation system in the country.

The Centro Nacional de Trasplantes (CENATRA), established in 2000, is responsible for promoting and coordinating the processes from donation to transplantation of organs, tissues, and cells in Mexico [3]. CENATRA seeks to increase organ donation and transplantation rates by optimizing existing resources and infrastructure for better coordination between donors and transplant centers and enhancing the skills of healthcare professionals.

According to CENATRA [3], in 2022, 19,555 people were waiting for an organ transplant in Mexico, of whom 15,028 were waiting for a kidney transplant from a deceased donor. These patients wait an average of 35.3 months to receive a transplant (while in the US programs, such as the National Kidney Registry, reported 1.8 months as median wait time to transplant in 2023 [4]). The kidney waiting list increases by 4-6% annually. Only 17.5% (2700) of candidates received a transplant in 2022, 1513 from living donors and 506 from deceased donors. In addition, the low brain-death donation rate (about 4.6 donors pmp [3], lower than rates reported in countries such as Argentina, Uruguay, the United States, and Spain [5]) results in a shortage of transplants. The two main reasons why potential deceased donors do not yield organs are family refusal (61.1%) and other issues such as logistical aspects and donor medical complications (30.9%) [3]. This highlights the need to promote a strong culture of donation and public awareness in the country. Living donation exceeds deceased donation in the country (about 13.64 donors pmp, according to the International Registry in Organ Donation and Transplantation [5]). At the same time, according to Martínez Calderón et al. [6], about 30% of patients on the waiting list have a potential but incompatible living donor.

Sánchez-Cedillo et al. [7] compared the costs of kidney replacement therapies versus transplantation at 1, 3, and 6 years, finding that the annual average costs per patient are about (USD) $24,844 for peritoneal dialysis, $33,455 for hemodialysis, and $21,813 for transplantation (considering the analyzed periods). Transplant costs are decreasing more quickly over the years than costs for peritoneal dialysis and hemodialysis. With approximately 15,000 transplant candidates waiting, the annual cost of renal replacement therapies exceeds $400 million, which is higher than the cost of transplanting all patients ($300 million). In addition, transplant offers patients and their families a better quality of life, and increases their labor force participation. A study by the Mexican Government [8] estimates an annual value at around $48,394 per person who returns to work.

The essential infrastructure for a successful KEP is outlined in the most recent CENATRA report [9]. Strategic priorities are reducing transplant waiting lists, strengthening logistics to prevent organ loss, activating underutilized transplant capacity through clinical brigades,

reinforcing state transplant centers, coordinating with prosecutors' offices in medico-legal cases, developing national registries for chronic diseases, and enhancing the National Transplant Information System with decision-support tools. Collectively, these priorities establish a strong foundation for a future KEP by improving the availability of transplant centers and their operational capacity, enabling coordinated organ transport for kidney exchanges, facilitating standardized data sharing and clinical coordination, and ensuring centralized governance under CENATRA that integrates public institutions, private providers, and philanthropic support within a unified national framework.

Optimization models and algorithms can increase the number of kidney transplants and enhance the related information systems that support transplant decision making. In Mexico, some healthcare institutions have implemented kidney exchanges; however, these have been isolated efforts, which are not part of a national KEP [10–13].

Contribution of the paper. In this work, we proposed a simulation process aimed to (a) determine if a KEP is feasible within the Mexican population, (b) estimate the potential number of incompatible pairs that will become available during a specific period, (c) determine the expected number of incompatible pairs that might be matched and transplanted in a KEP program. We assessed the potential impact of the program if it were implemented in Mexico by simulating three different scenarios.

This work is organized as follows. Section 2 describes the simulation. Section 3 details the results of the proposed approach and analyzes the impact of creating a national KEP under three different scenarios. Section 4 contains a discussion and future research lines.

2 Materials and methods

First, we explain the simulation process and the distributions used to estimate the data. Then, we briefly describe the optimization problem solved to find the optimal matching for the set of incompatible pairs generated during the simulation. Some of the required data depend on a complex interaction of population-level health indicators (e.g., rates of obesity, hypertension, diabetes, access to medical care), which can vary from country to country. We use for several cases the OPTN data as a reasonable approximation on distributions for exploratory purposes, given the similarities between the US and Mexico in health indicators and the limited availability of these data in Mexico at the national level.

2.1 Simulation

We simulate the number of incompatible donor-patient pairs that would arise during a year, according to blood type distributions of the Mexican population. This simulation follows steps S1-S4, based on the model of Zenios et al. [14].

S1. **Age assignment.** The first step is to assign the age for each patient: *Youth, Adult, or Older adult*. Second, for each group a donor-patient relationship is assigned based on the age distribution provided by the Organ Procurement and Transplantation Network (OPTN) [15]. We summarize this information into 6 categories for donors and 3 for patients (see Table A1 in Appendix A). The "Sibling" category contains the direct *Biological* categories from the OPTN report, while the *Other* category contains the "Biological, blood-related Other Relative", "Non-Biological, Life Partner" and "Non-Biological, Other Unrelated Directed". The "Not reported" and the "Unknown" categories from the report are not considered in this study. Finally, two donors from the donor candidate pool are randomly selected.

S2. **ABO group assignment.** An ABO blood group is assigned to patients and their potential donors according to the Mexican population's blood type distribution [16]. The blood type O is the most common group with 65% of the population, followed by type A (25%), B (8.6%), and AB (1.4%), respectively. In the case of children's blood types, it is required to know the parents' genotypes. The child's genotype will be a combination of two randomly selected alleles (one for each parent) determined by using the Hardy-Weinberg principle [17]. First,

a random genotype is assigned to the parents, spouse, and others, according to the distributions: AA (2.03%), AO (22.97%), AB (1.46%), BB(0.26%), BO (8.27%), OO (65.01%). Second, the genotypes of the patient and the siblings randomly inherit an allele from each parent: A (0.14%), B (0.05%), O (0.81%). Finally, the genotypes of children are determined, and then their blood type.

S3. **ABO and work-up tests.** The ABO compatibility is determined for each donor-recipient pair. A medical work-up is also simulated to assess the health and the decision to donate of donors. We discard 25% of spousal donors and 56.7% of other donors [14, 18], as there are several reasons for not accepting them [19]. For ABO-compatible donors who passed the work-up, a crossmatch test is performed (S4). If a donor is ABO incompatible or crossmatch-incompatible but passes the medical work-up, **the pair joins the exchange program pool**. In any other case, donors are non-viable and are not considered in the simulation.

S4. **Crossmatch test.** First, the sex of the patient is randomly assigned according to OPTN data from 1988 to 2017 [15], with 40% of patients being female. A Panel-Reactive Antibody (PRA) group is then assigned to the patient. The positive crossmatch rate varies depending on whether the patient is the wife or the mother of the donor since they are more likely to be sensitized to their husbands' and children's antigens, respectively (for overall weighted distribution and rates) [18].

Possible outcomes of the simulation are the following:

- **Direct donation**: If there is an ABO compatible donor who passed both medical workup and crossmatch test.
- **Exchange program**: If there is an ABO incompatible donor who passed the medical work-up; or an ABO compatible donor who passed the medical work-up but failed the crossmatch test. The obtained pool of donors and their recipients, is used in the optimization phase of Section 2.2 for a potential kidney exchange.
- **Non-viable donor**: Donors who failed the medical work-up.

Some assumptions are considered for the simulation:

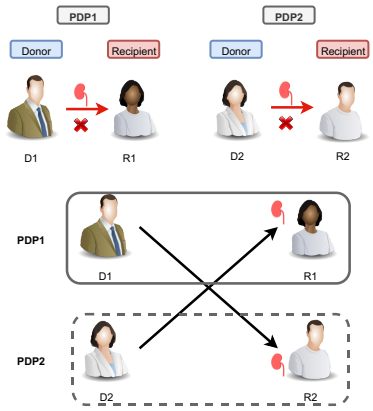
- Donors will donate their kidney if and only if their associated recipient obtains a compatible kidney through the exchange.
- Each donor/patient can donate/receive at most only one kidney.
- Except for the spouse, other candidate types can be selected twice.
- Patient is a *mother* when female and has a child as a donor.
- Patient is a *wife* when female and has a spouse as a donor.
- If none of the donors pass the medical workup, the patient will join the waiting list.
- If both potential donors are compatible, one of them is randomly selected as the final direct donor.
- If both donors pass the medical work-up but are incompatible with the patient (fail the blood test or crossmatch), only one of them is randomly selected to join the KEP.
- If both donors pass the medical work-up and only one of them is compatible with the patient (blood type/crossmatch), the compatible donor is considered for a direct transplant. The incompatible one is removed from the simulation.

2.2 Optimization of incompatible pairs

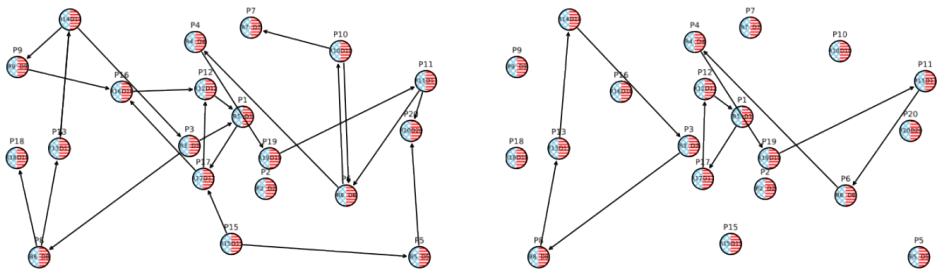
When kidneys from a given donor are not compatible, an *incompatible Patient-Donor Pair* (PDP) is formed (Figure 1a). A group of them is called a Kidney Exchange pool, which can be interpreted as a directed compatibility graph by associating one vertex Px to each PDP (see Figure 1b) [20]. A directed arc from one vertex Px to another Py, where x and y represent two

different PDPs, is added only if a donor *Dx* of the first pair is compatible (and can donate) with the patient *Ry* of P*y*. This arc may have a specific weight determined by a committee of healthcare professionals. Finally, a *cycle* in the graph represents a possible kidney swap of *k* PDPs, with *k* as the maximum number of simultaneous transplants, forming a *k*-way exchange (a cycle that contains *k* pairs).

Cycles are usually constrained in length as they involve 2*k* simultaneous surgeries, certain materials, and human resources, as well as considering some important logistics aspects. The solution (cycles) obtained after optimization (Figure 1c), represents the maximum number of transplants that can be potentially performed.



(a) 2-way kidney exchange



(b) Kidney exchange pool (c) Associated optimal solution

Fig. 1: Illustrative example of a 2-way kidney exchange, kidney exchange pool, and its associated solution.

Mathematically, the *Kidney Exchange problem* can be seen as a combinatorial optimization problem aimed at finding cycles of maximum cardinality (or a weighted maximum cardinality). We used the algorithm proposed by Dickerson et al. [21] to maximize the number of compatible patient-donor pairs obtained from the PDPs pool.

3 Results

3.1 Estimation of incompatible pairs

To estimate the number of incompatible pairs in a year, we generated new simulated pairs until 2,126 direct transplants were obtained. This is the number of LDKTs performed in Mexico in 2017. Once this number of directed transplants is reached, we can estimate the number of expected incompatible pairs that might join in a hypothetical KEP in a year. For comparison purposes, we also simulate the US population using the blood type frequencies from Zenios et al. [14], determined for the *Caucasians* group.

The average counts, based on a sample of 30 replications, obtained from both (Mexico/US) blood type distributions, are:

- **Total generated #Pairs:** 3,121 (Mexico) and 3,336 (US).
- **Pairs for direct transplant:** 2,126 (68.1%, Mexico) and 2,126 (63.7%, US).
- **Pairs for the KE program:** 995 (31.9%) and 1,210 (36.3%, US).
  - ABO incompatible: 500 (50.2%, Mexico) and 709 (58.6%, US)
  - Crossmatch test failure: 495 (49.8%, Mexico) and 501 (41.4%, US)

The simulation estimates an average of 995 incompatible pairs each year in Mexico, which is 31.9% of the total number of generated pairs. For incompatible pairs, an average of 50.2% joined the exchange program due to a blood type incompatibility; while 49.8% joined the program due to an unsatisfactory cross-match test. For the US results, an average of 1,210 are obtained; 58.6% of the incompatible pairs are due to blood type incompatibility.

3.2 Pool of incompatible pairs

We proceed to establish a pool of 995 incompatible pairs for both countries considering the probability distributions provided in Section 2.1. The outcomes are the average values computed across 30 repetitions.

Age and blood type distribution.

For both, Mexico and US, the largest proportion of patients falls within the *Adult* (50.2% Mex, 51.9% US) and *Older Adult* (43.2% Mex, 41.1% US) age groups; just about 7% of them (6.6% for Mex) fall within the *Young* category. Table 1 shows the resulting blood type distribution for both pools of incompatible donor/recipient pairs, where most of the recipients are blood type O.

3.3 Optimal matching

We will focus on optimizing the created pools to maximize the number of matched pairs, which represents the potential number of transplants to be performed. For this, we used the solution algorithm mentioned in Section 2, allowing only cycles of length $k = 2$. Optimization algorithms can efficiently solve 2-way matches [22], and in practice 2-way exchanges are more robust and operationally feasible in kidney exchange. Longer cycles can theoretically increase the number of transplants but are much more vulnerable to failure in practice [23], and finding them is computationally expensive.

We found an optimal matching of 624 pairs for the Mexican KEP simulation. We found an optimal matching of 562 pairs for the US simulation. Almost half of the matched pairs in the Mexican pool (47.4%, 294) belong to the blood group O, whereas for the US, blood types *A* and *O* were predominant (Table 1). For the Mexican pool, most of the unmatched pairs have a recipient with blood type O (93.3%), and only in one of them, the donor has blood type O (Table 1). For the US pool, most of the unmatched pairs have a recipient with blood type O (85.9%).

Matching rates are calculated by dividing the total number of matched pairs by the total number of pairs. Table 1 shows the matching rates for different blood type combinations. In both Mexican and US pools, the matching rate is higher when the donor is blood type O (99.7%) and recipients have blood type AB (87.5%). The lowest matching rate is for AB donors (6.5%) since they can only donate to recipients with AB.

Table 1: Donor/recipient distributions pairs in Mexican and US pools

		Mexico					US				
	Pairs[1]	dO	dA	dB	dAB	Total	dO	dA	dB	dAB	Total
Blood type	rO	29.8%	32.2%	10.9%	1.2%	**74.1%**	15.5%	33.9%	9.4%	1.8%	**60.6%**
	rA	6.7%	6.3%	3.2%	1.0%	**17.2%**	7.0%	12.2%	5.6%	3.0%	**27.8%**
	rB	2.8%	2.6%	1.7%	0.8%	**7.9%**	0.4%	5.1%	1.8%	2.6%	**9.9%**
	rAB	0.2%	0.4%	0.1%	0.1%	**0.8%**	0.3%	0.7%	0.3%	0.3%	**1.6%**
Total		**39.5%**	**41.5%**	**15.9%**	**3.1%**	**100.0%**	**23.2%**	**51.9%**	**17.1%**	**7.7%**	**100.0%**
% Matched pairs[2]	rO	47.4%	10.7%	4.5%	0.0%	**62.7%**	27.4%	12.6%	0.9%	0.2%	**41.1%**
	rA	10.6%	9.9%	4.8%	0.2%	**25.5%**	12.5%	21.4%	9.4%	0.7%	**44.0%**
	rB	4.5%	4.2%	1.9%	0.2%	**10.7%**	0.7%	9.1%	2.3%	0.2%	**12.3%**
	rAB	0.3%	0.6%	0.2%	0.0%	**1.1%**	0.5%	1.2%	0.5%	0.4%	**2.7%**
Total		**62.8%**	**25.4%**	**11.4%**	**0.4%**	**100.0%**	**41.1%**	**44.3%**	**13.1%**	**1.5%**	**100.0%**
Unmatched pairs	rO	0.3%	68.2%	21.6%	3.2%	**93.3%**	0.0%	61.4%	20.6%	3.9%	**85.9%**
	rA	0.0%	0.3%	0.5%	2.4%	**3.2%**	0.0%	0.2%	0.7%	6.0%	**7.0%**
	rB	0.0%	0.0%	1.3%	1.9%	**3.2%**	0.0%	0.0%	1.2%	5.8%	**6.9%**
	rAB	0.0%	0.0%	0.0%	0.3%	**0.3%**	0.0%	0.0%	0.0%	0.2%	**0.2%**
Total		**0.3%**	**68.5%**	**23.4%**	**7.8%**	**100.0%**	**0.0%**	**61.6%**	**22.5%**	**15.9%**	**100.0%**
Matched rates	rO	99.7%	20.9%	25.9%	0.0%	**53.1%**	100.0%	21.1%	5.3%	5.6%	**38.3%**
	rA	100.0%	98.4%	93.8%	10.0%	**93.0%**	100.0%	99.2%	94.6%	13.3%	**89.2%**
	rB	100.0%	100.0%	70.6%	12.5%	**84.8%**	100.0%	100.0%	72.2%	3.8%	**69.7%**
	rAB	100.0%	100.0%	100.0%	0.0%	**87.5%**	100.0%	100.0%	100.0%	66.7%	**93.8%**
Total		**99.7%**	**38.5%**	**44.9%**	**6.5%**		**100.0%**	**48.3%**	**43.3%**	**10.4%**	

[1] dX and rX denote donor and recipient blood types, respectively.
[2] Out of 624 matched pairs for Mexico and 562 matched pairs for US

3.4 Incompatible pairs in waiting list

We estimated the number of incompatible patient-donor pairs in the Mexican waiting list. The simulator randomly generates pairs until the number of pairs who join the exchange program plus the number of patients without a donor is equal to the number of patients on the waiting list (13,313 as of July 2017 [24]). This process was repeated 30 times, generating 13,313 cases of which, on average, 55.2% (7,351.5) corresponded to patients without a donor and 44.8% (5,961.5) to pairs who would be part of the KE program. Of the latter, 50.3% (2,996) had ABO incompatibility and 49.7% (2,965.5) failed the cross-match test.

3.5 Impact of a kidney exchange program in Mexico

To determine the potential impact of a KEP in Mexico, starting in 2018, we simulated the following three hypothetical scenarios based on the information provided in previous sections and some considerations from real-world KEPs and studies from the literature:

- **Scenario NKR (2018-2028):**
  - %New: 2-6 (+1% increase per year).
  - %WL: 2-6 (+1% increase per year).
  - %Matched: 20-65 (+5% increase/decrease per year).
  - %Proceed: 65-85 (+5% increase/decrease per year).
  - %Remains: 60
- **Scenario DKP (2018-2028):**
  - %New: 5 (2018), 6 (2019), 10 (2020), 12.5 (2021-2028).
  - %WL: 5 (2018), 6 (2019), 10 (2020), 12.5 (2021-2028).

- %Matched: 20-65 (+5% increase/decrease per year).
- %Proceed: 65-85 (+5% increase/decrease per year).
- %Remains: 40

• **Scenario MEX (2018-2028):**

- %New: 3.5-12.5 (+1% increase per year).
- %WL: 3.5-12.5 (+1% increase per year).
- %Matched: 20-65 (+5% increase/decrease per year).
- %Proceed: 10-65 (+5% increase/decrease per year).
- %Remains: 40

In the **NKR** case, we use some percentages obtained from the National Kidney Registry [4, 25]. This scenario highlights an initial small percentage of pairs who enter the program (ranging from 4 to 12%, which we have equally distributed between **%New** (new incompatible pairs who arise in the year) and **%WL** (new incompatible pairs who come from the waiting list). In addition, a percentage of matches between 20-65% and a percentage between 65-85% of transplants that proceed, are determined. We use a significant percentage of pairs who remain in the pool of 60% (%Remains) considering that 40% of recipients in the US waiting list are removed from the list for other reasons [15].

On the other hand, for the **DKP** scenario (derived from results of the Dutch Transplant Foundation [26]), we consider a higher percentage of entering pairs (10-25%, equally distributed between %New and %WL) and a lower percentage of pairs (40%) who remain in the program. The %Matched and %Proceed percentages remain the same as the NKR since the maximum reported values are quite similar.

Finally, for the **MEX** case, we establish a new scenario based on a moderate percentage of initial pairs entering the program (7-25%, evenly distributed between %New and %WL). The percentage of matched pairs who proceed to transplant is based on a study from the United Network for Organ Sharing (UNOS) [23], which found that at least 90% of the transplants were not performed for several reasons such as differences in sensitization levels, illness, and other medical or logistical challenges. The percentage of remaining pairs in the pool corresponds to the lowest value of the previous cases, reflecting a more complex initial situation in Mexico compared to the US and Dutch programs.

In our Mexican simulation, 63% of pairs are matched, which is similar to the maximum matching % of the NKR and DKP cases. We consider 65% as the maximum annual matching rate for all cases.

Figure 2 shows the comparison among scenarios, where:

- **New Incompatible Pairs** corresponds to the %New entering pairs per year.
- **Incompatible Pairs from WL** corresponds to the %WL pairs who enter the program from the waiting list.
- **Total pairs** is the sum of the %New plus %WL pairs of the corresponding year and the %Remain pairs from the last year.
- **Matched** considers the %Matched pairs from the current pool.
- **Transplanted** corresponds to the portion of matched pairs who proceed to transplant (%Proceed).
- **Remaining in pool** corresponds to a % of the current total (not transplanted) pairs who will remain in the pool of the corresponding year.
- **Remaining in WL** refers to the number of incompatible pairs who remain on the waiting list in the current year. This total includes WL pairs from the previous year and the new incompatible pairs added annually, excluding those who have been transplanted. Finally, 9.82% of those **Remaining in WL** are also removed due to other reasons that occurred in the real-world situation (medical issues, donor/recipient decease, etc.).

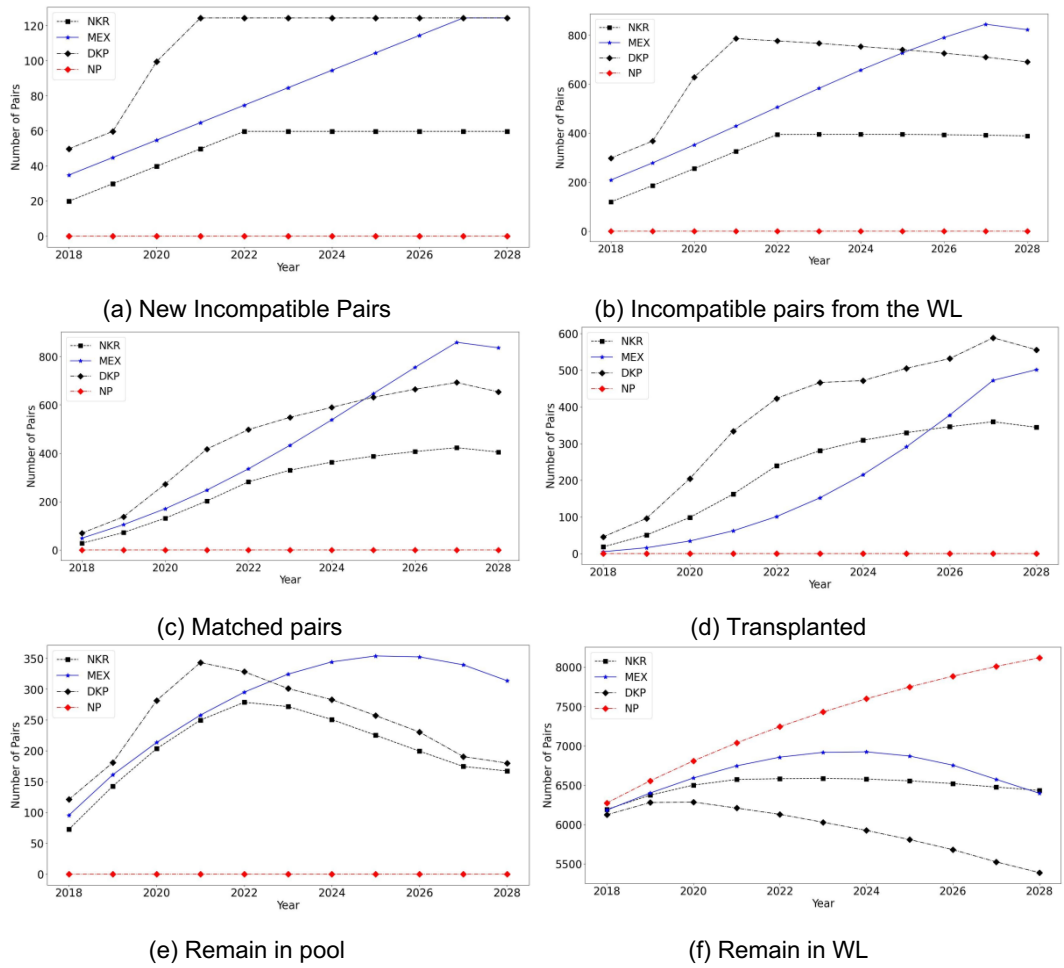


Fig. 2: Comparison among scenarios

In the DKP scenario (Figures 2a-2b), which corresponds to the highest beginning in terms of participation every year but the lowest level of persistence in the program, the number of matches increases each year (Figure 2c) and the number of transplants increases each year. This is largely due to the pairs who remain in the pool (although the DKP has the lowest level of persistence, the pool increases significantly during the first five years), showing that a high involvement of incompatible pairs at the beginning of the program can bring early benefits.

In the NKR scenario, having a high proportion of incompatible pairs who remain in the program counteracts the low participation at the beginning of the KEP. Although transplants are a little lower than in the DKP scenario, the NKR also shows increasing transplants.

For the MEX scenario, in which we have considered an intermediate initial participation with a linear upward trend, we can observe that the program grows significantly after 7 years, bringing the number of transplants up to be similar to the other scenarios. This is due to the low persistence in the pool and the low initial percentage of transplants.

Finally, all the proposed scenarios help to limit the number of incompatible pairs remaining on the waiting list, compared to the case where no KEP exists (Figure 2f).

3.5.1 Comparison with respect to the real-world situation in Mexico

Figure 3 shows the estimated number of Living Donor Kidney Transplants (LDKTs) into the future under various scenarios, and compared with current values provided by CENATRA from 2012 to 2023 [27]. This analysis aims to understand the long-term behavior and potential impact of the KEP in future years. Three different periods are considered:

- 2012-2017: Actual data from CENATRA for LDKTs.
- 2018-2023: Simulated scenarios vs real-world data from CENATRA.
- 2024-2028: Estimated data from the real-world case in Mexico vs simulated cases.

We model increases in the number of transplants beginning in 2018, when the program was modeled to start. In 2020, there was a major decrease in the number of LDKTs attributable to the COVID-19 pandemic.

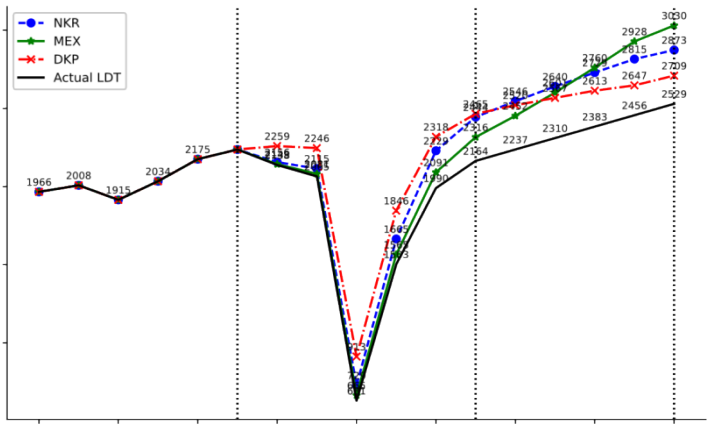


Fig. 3: Living-Donor Transplant per year

4 Discussion

Mexico's kidney transplant system does not generate enough deceased donors to transplant waiting patients. Comprehensive strategies including a KEP might increase the availability of kidneys and secure equitable access to transplantation. A KEP would increase the number of potential transplants by capturing more donations from living donors in incompatible patient-donor pairs.

We simulated the impact of implementing a national KEP in Mexico. We estimated that 995 incompatible pairs might arise in Mexico each year. Also, 5,961 patients on the waiting list (44.8%) would have an incompatible donor, and establishing a KEP in Mexico could identify compatible kidney transplants for these patients. The higher proportion of individuals with O blood type in Mexico increased the number of successful donor-recipient matches compared to other countries like the United States in our simulation.

Our simulation shows that a KEP would substantially benefit patients by increasing living donor kidney transplants in the subsequent years after its implementation. By increasing LDKT, this program may also help to stabilize the increase in the number of patients on the waiting list.

We considered several scenarios regarding the number of pairs that enter and leave the program, based on data published by the National Kidney Registry and the Dutch Transplant Foundation. The three scenarios offer a sensitivity analysis showing how these assumptions would impact the expected success of the program, achieving up to 20% more transplants. Comparing the scenarios highlights the importance of early participation of recipients and donors in the program, as well as retaining incompatible pairs in the pool; both of these levers increase the number of matches and transplants.

In the future, we urge Mexican institutions to collect data on medical work-up and cross-match test probabilities for the Mexican population. We did not analyze the effect of including compatible pairs in the program, nor altruistic non-directed donors and deceased donors. Non-directed living donors can begin *chains* of donation in the program which might over the longer

term become feasible in the Mexican setting. Furthermore, although longer cycles were not considered in this study, due to their vulnerability to pre-match failures, we recognize their theoretical relevance and suggest including them as a future line of research. Finally, we could model or test new policies and transplant mechanisms that have been applied in Chile [28, 29].

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Competing interests. The authors of this manuscript have a potential conflict of interest to disclose: Sommer Gentry reports a relationship with Hennepin Healthcare Research Institute that includes: employment. She is a Senior Investigator with the Scientific Registry of Transplant Recipients. The remaining authors declare that they have no conflicts of interest to disclose.

The authors confirm that the data supporting the findings of this study are available in the article and/or its supplementary materials.

Author contribution. RZRM, MAHM, and DLHM conceived the study and acquired funding. MAHM and DLHM collected data. RZRM, MAHM and DLHM wrote the original draft manuscript. Supervision: RZRM, SEG, and HAZC. All authors analyzed the data, critically reviewed, edited, and approved the final manuscript.

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Appendix A Complementary Tables

Table A1: US Transplants: January 1, 1988 - May 31, 2017 (OPTN, June 19, 2017)

Patient age / Donor relation (%)	Youths <17	Adults 18-49	Older adults 50+	Total
Parent	7,064 (75.2%)	11,317 (15.7%)	102 (0.2%)	18,483 (14.0%)
Child	0 (0.0%)	3,251 (4.5%)	18,936 (37.6%)	22,187 (16.8%)
Sibling	668 (7.1%)	31,970 (44.3%)	9,704 (19.3%)	42,342 (32.1%)
Spouse	0 (0.0%)	7,784 (10.8%)	7,426 (14.7%)	15,210 (11.5%)
Other	1,666 (17.7%)	17,854 (24.7%)	14,239 (28.3%)	33,759 (25.6%)
Total	9,398 (100%)	72,176 (100%)	50,407 (100%)	131,981 (100%)
Age distribution	**7.1%**	**54.7%**	**38.2%**	**100%**

Assessing the Potential Impact of a Kidney Exchange Program in Mexico

Short running title: Potential Impact of a KEP in Mexico

Keywords: Kidney disease, Kidney exchange program, Simulation, Optimization

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Title of Journal, abbreviated as in reference list. Clin Transplant

List of abbreviations for the article

CENATRA, Centro Nacional de Trasplantes
DKP, Dutch Kidney Program
ESRD, End-Stage Renal Disease
HLA, Human Leukocyte Antigen
KEP, Kidney Exchange Program
LDKT, Living Donor Kidney Transplantation
NKR, National Kidney Registry
OPTN, Organ Procurement and Transplantation Network
PDP, Patient-Donor Pair
PRA, Panel-Reactive Antibody
UNOS, United Network for Organ Sharing
pmp, per million population
WL, Waiting List

Abstract

Introduction: In Mexico, more than 15,000 patients are waiting for a kidney transplant, and there are not enough kidneys from deceased donors to transplant them. A kidney exchange program could increase kidney transplants from living donors by matching altruistic living donors and biologically incompatible donor-recipient pairs. Several countries have implemented successful kidney exchange programs. We evaluated the impact of implementing a kidney exchange program in Mexico.
Methods: We simulated kidney exchange in Mexico using data from Mexican population distributions. We used an optimization model to maximize the number of compatible patient-donor matchings. Three different scenarios were evaluated.
Results: We estimated that almost 45% of patients on the waiting list have an incompatible donor, and 995 transplant candidates who have a living donor available are added to the waiting list annually. If a kidney exchange program were established in Mexico, the number of living-donor transplants could increase by up to 20%.
Conclusions: Implementing kidney exchange in the country may reduce the increase in the number of recipients on the waiting list and reduce costs in the long term. To succeed, the program must not only draw sufficient participation from incompatible pairs, but also ensure that these pairs remain in the program even if they have to wait to be matched.

Keywords. Kidney disease, Kidney exchange program, Simulation, Optimization

Name and address of the author to whom requests for offprints should be sent.
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1 Introduction

Many patients who need a kidney transplant can identify a living donor. A Living Donor Kidney Transplantation (LDKT) is considered the best treatment choice for patients with end-stage renal disease (ESRD) as it provides greater long-term survival rates and a better quality of life. LDKT can include preoperative desensitization in case of ABO blood type or human leukocyte antigen (HLA) incompatibility [1]. However, LDKT requires finding a compatible donor. When a patient's intended living donor, who is commonly a relative of the recipient, is not compatible with their patient, a kidney exchange transplantation can be an alternative.

A Kidney Exchange Program (KEP) has been implemented in several countries to match incompatible donor-recipient pairs for a kidney exchange transplantation [2]. Although KEPs have provided successful results in different countries, in Mexico there is no such a program at a national level, though a few kidney exchanges have been performed in Mexico. In this work, we analyze the impact of implementing a KEP in Mexico with a simulation using blood type distributions obtained from the Mexican population.

1.1 Kidney transplantation in Mexico

In Mexico, the first organ transplant was performed in 1963 with no pre-existing legislation. The first regulation was created in the Código Sanitario de los Estados Unidos Mexicanos in 1973. Since then, several laws, modifications, and collaborations have been carried out to improve and regulate the organ transplantation system in the country.

The Centro Nacional de Trasplantes (CENATRA), established in 2000, is responsible for promoting and coordinating the processes from donation to transplantation of organs, tissues, and cells in Mexico [3]. CENATRA seeks to increase organ donation and transplantation rates by optimizing existing resources and infrastructure for better coordination between donors and transplant centers and enhancing the skills of healthcare professionals.

According to CENATRA [3], in 2022, 19,555 people were waiting for an organ transplant in Mexico, of whom 15,028 were waiting for a kidney transplant from a deceased donor. These patients wait an average of 35.3 months to receive a transplant (while in the US programs, such as the National Kidney Registry, reported 1.8 months as median wait time to transplant in 2023 [4]). The kidney waiting list increases by 4-6% annually. Only 17.5% (2700) of candidates received a transplant in 2022, 1513 from living donors and 506 from deceased donors. In addition, the low brain-death donation rate (about 4.6 donors pmp [3], lower than rates reported in countries such as Argentina, Uruguay, the United States, and Spain [5]) results in a shortage of transplants. The two main reasons why potential deceased donors do not yield organs are family refusal (61.1%) and other issues such as logistical aspects and donor medical complications (30.9%) [3]. This highlights the need to promote a strong culture of donation and public awareness in the country. Living donation exceeds deceased donation in the country (about 13.64 donors pmp, according to the International Registry in Organ Donation and Transplantation [5]). At the same time, according to Martínez Calderón et al. [6], about 30% of patients on the waiting list have a potential but incompatible living donor.

Sánchez-Cedillo et al. [7] compared the costs of kidney replacement therapies versus transplantation at 1, 3, and 6 years, finding that the annual average costs per patient are about (USD) $24,844 for peritoneal dialysis, $33,455 for hemodialysis, and $21,813 for transplantation (considering the analyzed periods). Transplant costs are decreasing more quickly over the years than costs for peritoneal dialysis and hemodialysis. With approximately 15,000 transplant candidates waiting, the annual cost of renal replacement therapies exceeds $400 million, which is higher than the cost of transplanting all patients ($300 million). In addition, transplant offers patients and their families a better quality of life, and increases their labor force participation. A study by the Mexican Government [8] estimates an annual value at around $48,394 per person who returns to work.

The essential infrastructure for a successful KEP is outlined in the most recent CENATRA report [9]. Strategic priorities are reducing transplant waiting lists, strengthening logistics to prevent organ loss, activating underutilized transplant capacity through clinical brigades,

reinforcing state transplant centers, coordinating with prosecutors' offices in medico-legal cases, developing national registries for chronic diseases, and enhancing the National Transplant Information System with decision-support tools. Collectively, these priorities establish a strong foundation for a future KEP by improving the availability of transplant centers and their operational capacity, enabling coordinated organ transport for kidney exchanges, facilitating standardized data sharing and clinical coordination, and ensuring centralized governance under CENATRA that integrates public institutions, private providers, and philanthropic support within a unified national framework.

Optimization models and algorithms can increase the number of kidney transplants and enhance the related information systems that support transplant decision making. In Mexico, some healthcare institutions have implemented kidney exchanges; however, these have been isolated efforts, which are not part of a national KEP [10–13].

Contribution of the paper. In this work, we proposed a simulation process aimed to (a) determine if a KEP is feasible within the Mexican population, (b) estimate the potential number of incompatible pairs that will become available during a specific period, (c) determine the expected number of incompatible pairs that might be matched and transplanted in a KEP program. We assessed the potential impact of the program if it were implemented in Mexico by simulating three different scenarios.

This work is organized as follows. Section 2 describes the simulation. Section 3 details the results of the proposed approach and analyzes the impact of creating a national KEP under three different scenarios. Section 4 contains a discussion and future research lines.

2 Materials and methods

First, we explain the simulation process and the distributions used to estimate the data. Then, we briefly describe the optimization problem solved to find the optimal matching for the set of incompatible pairs generated during the simulation. Some of the required data depend on a complex interaction of population-level health indicators (e.g., rates of obesity, hypertension, diabetes, access to medical care), which can vary from country to country. We use for several cases the OPTN data as a reasonable approximation on distributions for exploratory purposes, given the similarities between the US and Mexico in health indicators and the limited availability of these data in Mexico at the national level.

2.1 Simulation

We simulate the number of incompatible donor-patient pairs that would arise during a year, according to blood type distributions of the Mexican population. This simulation follows steps S1-S4, based on the model of Zenios et al. [14].

S1. **Age assignment.** The first step is to assign the age for each patient: *Youth, Adult, or Older adult*. Second, for each group a donor-patient relationship is assigned based on the age distribution provided by the Organ Procurement and Transplantation Network (OPTN) [15]. We summarize this information into 6 categories for donors and 3 for patients (see Table A1 in Appendix A). The "Sibling" category contains the direct *Biological* categories from the OPTN report, while the *Other* category contains the "Biological, blood-related Other Relative", "Non-Biological, Life Partner" and "Non-Biological, Other Unrelated Directed". The "Not reported" and the "Unknown" categories from the report are not considered in this study. Finally, two donors from the donor candidate pool are randomly selected.

S2. **ABO group assignment.** An ABO blood group is assigned to patients and their potential donors according to the Mexican population's blood type distribution [16]. The blood type O is the most common group with 65% of the population, followed by type A (25%), B (8.6%), and AB (1.4%), respectively. In the case of children's blood types, it is required to know the parents' genotypes. The child's genotype will be a combination of two randomly selected alleles (one for each parent) determined by using the Hardy-Weinberg principle [17]. First,

a random genotype is assigned to the parents, spouse, and others, according to the distributions: AA (2.03%), AO (22.97%), AB (1.46%), BB(0.26%), BO (8.27%), OO (65.01%). Second, the genotypes of the patient and the siblings randomly inherit an allele from each parent: A (0.14%), B (0.05%), O (0.81%). Finally, the genotypes of children are determined, and then their blood type.

S3. **ABO and work-up tests.** The ABO compatibility is determined for each donor-recipient pair. A medical work-up is also simulated to assess the health and the decision to donate of donors. We discard 25% of spousal donors and 56.7% of other donors [14, 18], as there are several reasons for not accepting them [19]. For ABO-compatible donors who passed the work-up, a crossmatch test is performed (S4). If a donor is ABO incompatible or crossmatch-incompatible but passes the medical work-up, **the pair joins the exchange program pool**. In any other case, donors are non-viable and are not considered in the simulation.

S4. **Crossmatch test.** First, the sex of the patient is randomly assigned according to OPTN data from 1988 to 2017 [15], with 40% of patients being female. A Panel-Reactive Antibody (PRA) group is then assigned to the patient. The positive crossmatch rate varies depending on whether the patient is the wife or the mother of the donor since they are more likely to be sensitized to their husbands' and children's antigens, respectively (for overall weighted distribution and rates) [18].

Possible outcomes of the simulation are the following:

- **Direct donation**: If there is an ABO compatible donor who passed both medical workup and crossmatch test.
- **Exchange program**: If there is an ABO incompatible donor who passed the medical work-up; or an ABO compatible donor who passed the medical work-up but failed the crossmatch test. The obtained pool of donors and their recipients, is used in the optimization phase of Section 2.2 for a potential kidney exchange.
- **Non-viable donor**: Donors who failed the medical work-up.

Some assumptions are considered for the simulation:

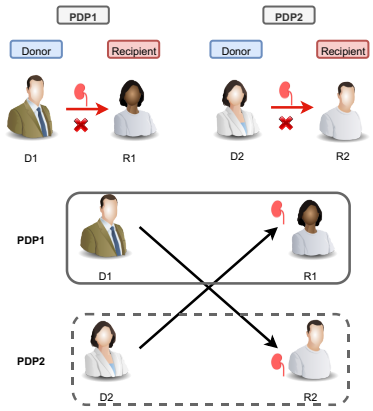
- Donors will donate their kidney if and only if their associated recipient obtains a compatible kidney through the exchange.
- Each donor/patient can donate/receive at most only one kidney.
- Except for the spouse, other candidate types can be selected twice.
- Patient is a *mother* when female and has a child as a donor.
- Patient is a *wife* when female and has a spouse as a donor.
- If none of the donors pass the medical workup, the patient will join the waiting list.
- If both potential donors are compatible, one of them is randomly selected as the final direct donor.
- If both donors pass the medical work-up but are incompatible with the patient (fail the blood test or crossmatch), only one of them is randomly selected to join the KEP.
- If both donors pass the medical work-up and only one of them is compatible with the patient (blood type/crossmatch), the compatible donor is considered for a direct transplant. The incompatible one is removed from the simulation.

2.2 Optimization of incompatible pairs

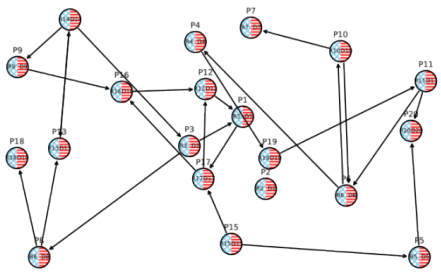
When kidneys from a given donor are not compatible, an *incompatible Patient-Donor Pair* (PDP) is formed (Figure 1a). A group of them is called a Kidney Exchange pool, which can be interpreted as a directed compatibility graph by associating one vertex Px to each PDP (see Figure 1b) [20]. A directed arc from one vertex Px to another Py, where x and y represent two

different PDPs, is added only if a donor *Dx* of the first pair is compatible (and can donate) with the patient *Ry* of P*y*. This arc may have a specific weight determined by a committee of healthcare professionals. Finally, a *cycle* in the graph represents a possible kidney swap of *k* PDPs, with *k* as the maximum number of simultaneous transplants, forming a *k*-way exchange (a cycle that contains *k* pairs).

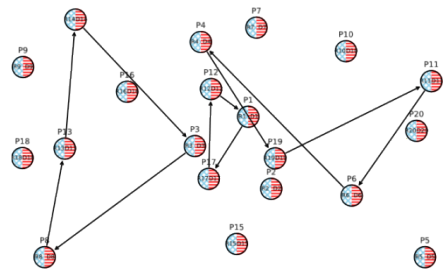
Cycles are usually constrained in length as they involve 2*k* simultaneous surgeries, certain materials, and human resources, as well as considering some important logistics aspects. The solution (cycles) obtained after optimization (Figure 1c), represents the maximum number of transplants that can be potentially performed.



(a) 2-way kidney exchange



(b) Kidney exchange pool



(c) Associated optimal solution

Fig. 1: Illustrative example of a 2-way kidney exchange, kidney exchange pool, and its associated solution.

Mathematically, the *Kidney Exchange problem* can be seen as a combinatorial optimization problem aimed at finding cycles of maximum cardinality (or a weighted maximum cardinality). We used the algorithm proposed by Dickerson et al. [21] to maximize the number of compatible patient-donor pairs obtained from the PDPs pool.

3 Results

3.1 Estimation of incompatible pairs

To estimate the number of incompatible pairs in a year, we generated new simulated pairs until 2,126 direct transplants were obtained. This is the number of LDKTs performed in Mexico in 2017. Once this number of directed transplants is reached, we can estimate the number of expected incompatible pairs that might join in a hypothetical KEP in a year. For comparison purposes, we also simulate the US population using the blood type frequencies from Zenios et al. [14], determined for the *Caucasians* group.

The average counts, based on a sample of 30 replications, obtained from both (Mexico/US) blood type distributions, are:

- **Total generated #Pairs:** 3,121 (Mexico) and 3,336 (US).
- **Pairs for direct transplant:** 2,126 (68.1%, Mexico) and 2,126 (63.7%, US).
- **Pairs for the KE program:** 995 (31.9%) and 1,210 (36.3%, US).
  - ABO incompatible: 500 (50.2%, Mexico) and 709 (58.6%, US)
  - Crossmatch test failure: 495 (49.8%, Mexico) and 501 (41.4%, US)

The simulation estimates an average of 995 incompatible pairs each year in Mexico, which is 31.9% of the total number of generated pairs. For incompatible pairs, an average of 50.2% joined the exchange program due to a blood type incompatibility; while 49.8% joined the program due to an unsatisfactory cross-match test. For the US results, an average of 1,210 are obtained; 58.6% of the incompatible pairs are due to blood type incompatibility.

3.2 Pool of incompatible pairs

We proceed to establish a pool of 995 incompatible pairs for both countries considering the probability distributions provided in Section 2.1. The outcomes are the average values computed across 30 repetitions.

Age and blood type distribution.

For both, Mexico and US, the largest proportion of patients falls within the *Adult* (50.2% Mex, 51.9% US) and *Older Adult* (43.2% Mex, 41.1% US) age groups; just about 7% of them (6.6% for Mex) fall within the *Young* category. Table 1 shows the resulting blood type distribution for both pools of incompatible donor/recipient pairs, where most of the recipients are blood type O.

3.3 Optimal matching

We will focus on optimizing the created pools to maximize the number of matched pairs, which represents the potential number of transplants to be performed. For this, we used the solution algorithm mentioned in Section 2, allowing only cycles of length $k = 2$. Optimization algorithms can efficiently solve 2-way matches [22], and in practice 2-way exchanges are more robust and operationally feasible in kidney exchange. Longer cycles can theoretically increase the number of transplants but are much more vulnerable to failure in practice [23], and finding them is computationally expensive.

We found an optimal matching of 624 pairs for the Mexican KEP simulation. We found an optimal matching of 562 pairs for the US simulation. Almost half of the matched pairs in the Mexican pool (47.4%, 294) belong to the blood group O, whereas for the US, blood types *A* and *O* were predominant (Table 1). For the Mexican pool, most of the unmatched pairs have a recipient with blood type O (93.3%), and only in one of them, the donor has blood type O (Table 1). For the US pool, most of the unmatched pairs have a recipient with blood type O (85.9%).

Matching rates are calculated by dividing the total number of matched pairs by the total number of pairs. Table 1 shows the matching rates for different blood type combinations. In both Mexican and US pools, the matching rate is higher when the donor is blood type O (99.7%) and recipients have blood type AB (87.5%). The lowest matching rate is for AB donors (6.5%) since they can only donate to recipients with AB.

Table 1: Donor/recipient distributions pairs in Mexican and US pools

		Mexico					US				
	Pairs[1]	dO	dA	dB	dAB	Total	dO	dA	dB	dAB	Total
Blood type	rO	29.8%	32.2%	10.9%	1.2%	**74.1%**	15.5%	33.9%	9.4%	1.8%	**60.6%**
	rA	6.7%	6.3%	3.2%	1.0%	**17.2%**	7.0%	12.2%	5.6%	3.0%	**27.8%**
	rB	2.8%	2.6%	1.7%	0.8%	**7.9%**	0.4%	5.1%	1.8%	2.6%	**9.9%**
	rAB	0.2%	0.4%	0.1%	0.1%	**0.8%**	0.3%	0.7%	0.3%	0.3%	**1.6%**
Total		**39.5%**	**41.5%**	**15.9%**	**3.1%**	**100.0%**	**23.2%**	**51.9%**	**17.1%**	**7.7%**	**100.0%**
% Matched pairs[2]	rO	47.4%	10.7%	4.5%	0.0%	**62.7%**	27.4%	12.6%	0.9%	0.2%	**41.1%**
	rA	10.6%	9.9%	4.8%	0.2%	**25.5%**	12.5%	21.4%	9.4%	0.7%	**44.0%**
	rB	4.5%	4.2%	1.9%	0.2%	**10.7%**	0.7%	9.1%	2.3%	0.2%	**12.3%**
	rAB	0.3%	0.6%	0.2%	0.0%	**1.1%**	0.5%	1.2%	0.5%	0.4%	**2.7%**
Total		**62.8%**	**25.4%**	**11.4%**	**0.4%**	**100.0%**	**41.1%**	**44.3%**	**13.1%**	**1.5%**	**100.0%**
Unmatched pairs	rO	0.3%	68.2%	21.6%	3.2%	**93.3%**	0.0%	61.4%	20.6%	3.9%	**85.9%**
	rA	0.0%	0.3%	0.5%	2.4%	**3.2%**	0.0%	0.2%	0.7%	6.0%	**7.0%**
	rB	0.0%	0.0%	1.3%	1.9%	**3.2%**	0.0%	0.0%	1.2%	5.8%	**6.9%**
	rAB	0.0%	0.0%	0.0%	0.3%	**0.3%**	0.0%	0.0%	0.0%	0.2%	**0.2%**
Total		**0.3%**	**68.5%**	**23.4%**	**7.8%**	**100.0%**	**0.0%**	**61.6%**	**22.5%**	**15.9%**	**100.0%**
Matched rates	rO	99.7%	20.9%	25.9%	0.0%	**53.1%**	100.0%	21.1%	5.3%	5.6%	**38.3%**
	rA	100.0%	98.4%	93.8%	10.0%	**93.0%**	100.0%	99.2%	94.6%	13.3%	**89.2%**
	rB	100.0%	100.0%	70.6%	12.5%	**84.8%**	100.0%	100.0%	72.2%	3.8%	**69.7%**
	rAB	100.0%	100.0%	100.0%	0.0%	**87.5%**	100.0%	100.0%	100.0%	66.7%	**93.8%**
Total		**99.7%**	**38.5%**	**44.9%**	**6.5%**		**100.0%**	**48.3%**	**43.3%**	**10.4%**	

[1] dX and rX denote donor and recipient blood types, respectively.
[2] Out of 624 matched pairs for Mexico and 562 matched pairs for US

3.4 Incompatible pairs in waiting list

We estimated the number of incompatible patient-donor pairs in the Mexican waiting list. The simulator randomly generates pairs until the number of pairs who join the exchange program plus the number of patients without a donor is equal to the number of patients on the waiting list (13,313 as of July 2017 [24]). This process was repeated 30 times, generating 13,313 cases of which, on average, 55.2% (7,351.5) corresponded to patients without a donor and 44.8% (5,961.5) to pairs who would be part of the KE program. Of the latter, 50.3% (2,996) had ABO incompatibility and 49.7% (2,965.5) failed the cross-match test.

3.5 Impact of a kidney exchange program in Mexico

To determine the potential impact of a KEP in Mexico, starting in 2018, we simulated the following three hypothetical scenarios based on the information provided in previous sections and some considerations from real-world KEPs and studies from the literature:

- **Scenario NKR (2018-2028):**
  - %New: 2-6 (+1% increase per year).
  - %WL: 2-6 (+1% increase per year).
  - %Matched: 20-65 (+5% increase/decrease per year).
  - %Proceed: 65-85 (+5% increase/decrease per year).
  - %Remains: 60
- **Scenario DKP (2018-2028):**
  - %New: 5 (2018), 6 (2019), 10 (2020), 12.5 (2021-2028).
  - %WL: 5 (2018), 6 (2019), 10 (2020), 12.5 (2021-2028).

- %Matched: 20-65 (+5% increase/decrease per year).
- %Proceed: 65-85 (+5% increase/decrease per year).
- %Remains: 40

• **Scenario MEX (2018-2028):**

- %New: 3.5-12.5 (+1% increase per year).
- %WL: 3.5-12.5 (+1% increase per year).
- %Matched: 20-65 (+5% increase/decrease per year).
- %Proceed: 10-65 (+5% increase/decrease per year).
- %Remains: 40

In the **NKR** case, we use some percentages obtained from the National Kidney Registry [4, 25]. This scenario highlights an initial small percentage of pairs who enter the program (ranging from 4 to 12%, which we have equally distributed between **%New** (new incompatible pairs who arise in the year) and **%WL** (new incompatible pairs who come from the waiting list). In addition, a percentage of matches between 20-65% and a percentage between 65-85% of transplants that proceed, are determined. We use a significant percentage of pairs who remain in the pool of 60% (%Remains) considering that 40% of recipients in the US waiting list are removed from the list for other reasons [15].

On the other hand, for the **DKP** scenario (derived from results of the Dutch Transplant Foundation [26]), we consider a higher percentage of entering pairs (10-25%, equally distributed between %New and %WL) and a lower percentage of pairs (40%) who remain in the program. The %Matched and %Proceed percentages remain the same as the NKR since the maximum reported values are quite similar.

Finally, for the **MEX** case, we establish a new scenario based on a moderate percentage of initial pairs entering the program (7-25%, evenly distributed between %New and %WL). The percentage of matched pairs who proceed to transplant is based on a study from the United Network for Organ Sharing (UNOS) [23], which found that at least 90% of the transplants were not performed for several reasons such as differences in sensitization levels, illness, and other medical or logistical challenges. The percentage of remaining pairs in the pool corresponds to the lowest value of the previous cases, reflecting a more complex initial situation in Mexico compared to the US and Dutch programs.

In our Mexican simulation, 63% of pairs are matched, which is similar to the maximum matching % of the NKR and DKP cases. We consider 65% as the maximum annual matching rate for all cases.

Figure 2 shows the comparison among scenarios, where:

- **New Incompatible Pairs** corresponds to the %New entering pairs per year.
- **Incompatible Pairs from WL** corresponds to the %WL pairs who enter the program from the waiting list.
- **Total pairs** is the sum of the %New plus %WL pairs of the corresponding year and the %Remain pairs from the last year.
- **Matched** considers the %Matched pairs from the current pool.
- **Transplanted** corresponds to the portion of matched pairs who proceed to transplant (%Proceed).
- **Remaining in pool** corresponds to a % of the current total (not transplanted) pairs who will remain in the pool of the corresponding year.
- **Remaining in WL** refers to the number of incompatible pairs who remain on the waiting list in the current year. This total includes WL pairs from the previous year and the new incompatible pairs added annually, excluding those who have been transplanted. Finally, 9.82% of those **Remaining in WL** are also removed due to other reasons that occurred in the real-world situation (medical issues, donor/recipient decease, etc.).

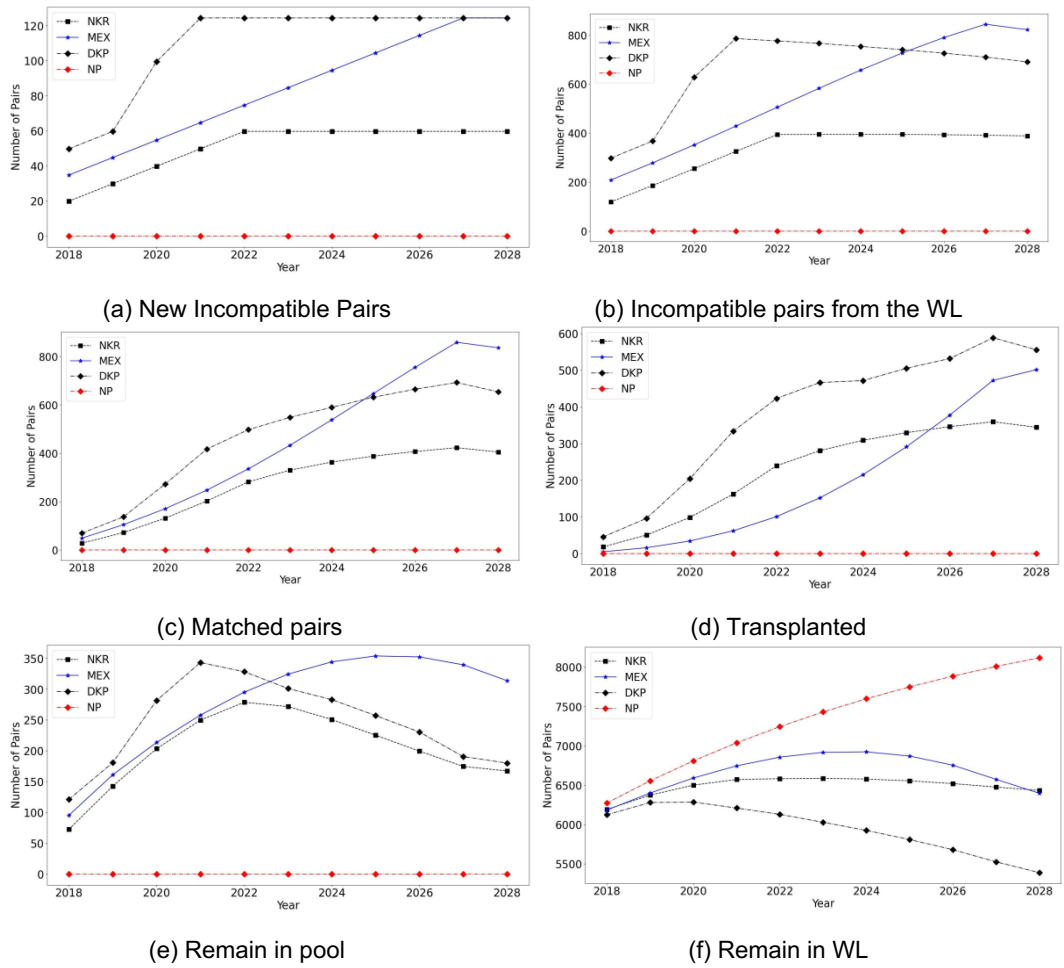


Fig. 2: Comparison among scenarios

In the DKP scenario (Figures 2a-2b), which corresponds to the highest beginning in terms of participation every year but the lowest level of persistence in the program, the number of matches increases each year (Figure 2c) and the number of transplants increases each year. This is largely due to the pairs who remain in the pool (although the DKP has the lowest level of persistence, the pool increases significantly during the first five years), showing that a high involvement of incompatible pairs at the beginning of the program can bring early benefits.

In the NKR scenario, having a high proportion of incompatible pairs who remain in the program counteracts the low participation at the beginning of the KEP. Although transplants are a little lower than in the DKP scenario, the NKR also shows increasing transplants.

For the MEX scenario, in which we have considered an intermediate initial participation with a linear upward trend, we can observe that the program grows significantly after 7 years, bringing the number of transplants up to be similar to the other scenarios. This is due to the low persistence in the pool and the low initial percentage of transplants.

Finally, all the proposed scenarios help to limit the number of incompatible pairs remaining on the waiting list, compared to the case where no KEP exists (Figure 2f).

3.5.1 Comparison with respect to the real-world situation in Mexico

Figure 3 shows the estimated number of Living Donor Kidney Transplants (LDKTs) into the future under various scenarios, and compared with current values provided by CENATRA from 2012 to 2023 [27]. This analysis aims to understand the long-term behavior and potential impact of the KEP in future years. Three different periods are considered:

- 2012-2017: Actual data from CENATRA for LDKTs.
- 2018-2023: Simulated scenarios vs real-world data from CENATRA.
- 2024-2028: Estimated data from the real-world case in Mexico vs simulated cases.

We model increases in the number of transplants beginning in 2018, when the program was modeled to start. In 2020, there was a major decrease in the number of LDKTs attributable to the COVID-19 pandemic.

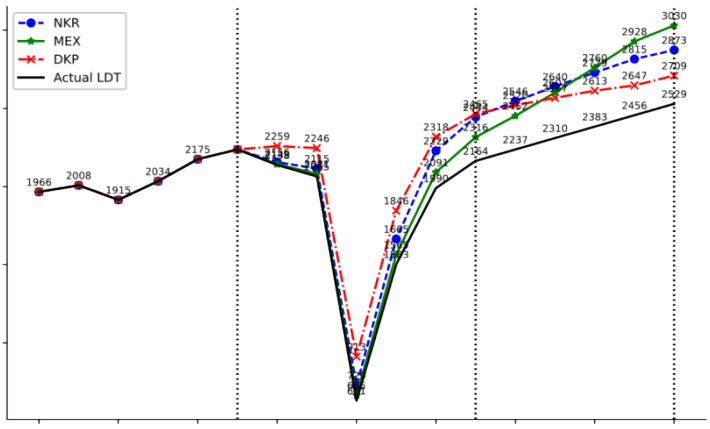


Fig. 3: Living-Donor Transplant per year

4 Discussion

Mexico's kidney transplant system does not generate enough deceased donors to transplant waiting patients. Comprehensive strategies including a KEP might increase the availability of kidneys and secure equitable access to transplantation. A KEP would increase the number of potential transplants by capturing more donations from living donors in incompatible patient-donor pairs.

We simulated the impact of implementing a national KEP in Mexico. We estimated that 995 incompatible pairs might arise in Mexico each year. Also, 5,961 patients on the waiting list (44.8%) would have an incompatible donor, and establishing a KEP in Mexico could identify compatible kidney transplants for these patients. The higher proportion of individuals with O blood type in Mexico increased the number of successful donor-recipient matches compared to other countries like the United States in our simulation.

Our simulation shows that a KEP would substantially benefit patients by increasing living donor kidney transplants in the subsequent years after its implementation. By increasing LDKT, this program may also help to stabilize the increase in the number of patients on the waiting list.

We considered several scenarios regarding the number of pairs that enter and leave the program, based on data published by the National Kidney Registry and the Dutch Transplant Foundation. The three scenarios offer a sensitivity analysis showing how these assumptions would impact the expected success of the program, achieving up to 20% more transplants. Comparing the scenarios highlights the importance of early participation of recipients and donors in the program, as well as retaining incompatible pairs in the pool; both of these levers increase the number of matches and transplants.

In the future, we urge Mexican institutions to collect data on medical work-up and cross-match test probabilities for the Mexican population. We did not analyze the effect of including compatible pairs in the program, nor altruistic non-directed donors and deceased donors. Non-directed living donors can begin *chains* of donation in the program which might over the longer

term become feasible in the Mexican setting. Furthermore, although longer cycles were not considered in this study, due to their vulnerability to pre-match failures, we recognize their theoretical relevance and suggest including them as a future line of research. Finally, we could model or test new policies and transplant mechanisms that have been applied in Chile [28, 29].

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Competing interests. The authors of this manuscript have a potential conflict of interest to disclose: Sommer Gentry reports a relationship with Hennepin Healthcare Research Institute that includes: employment. She is a Senior Investigator with the Scientific Registry of Transplant Recipients. The remaining authors declare that they have no conflicts of interest to disclose.

The authors confirm that the data supporting the findings of this study are available in the article and/or its supplementary materials.

Author contribution. RZRM, MAHM, and DLHM conceived the study and acquired funding. MAHM and DLHM collected data. RZRM, MAHM and DLHM wrote the original draft manuscript. Supervision: RZRM, SEG, and HAZC. All authors analyzed the data, critically reviewed, edited, and approved the final manuscript.

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Appendix A Complementary Tables

Table A1: US Transplants: January 1, 1988 - May 31, 2017 (OPTN, June 19, 2017)

Patient age / Donor relation (%)	Youths <17	Adults 18-49	Older adults 50+	Total
Parent	7,064 (75.2%)	11,317 (15.7%)	102 (0.2%)	18,483 (14.0%)
Child	0 (0.0%)	3,251 (4.5%)	18,936 (37.6%)	22,187 (16.8%)
Sibling	668 (7.1%)	31,970 (44.3%)	9,704 (19.3%)	42,342 (32.1%)
Spouse	0 (0.0%)	7,784 (10.8%)	7,426 (14.7%)	15,210 (11.5%)
Other	1,666 (17.7%)	17,854 (24.7%)	14,239 (28.3%)	33,759 (25.6%)
Total	9,398 (100%)	72,176 (100%)	50,407 (100%)	131,981 (100%)
Age distribution	**7.1%**	**54.7%**	**38.2%**	**100%**

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Response to Editor in Chief

General overview.
Please find an experienced native English writer to go over the paper and abstract line by line to make the minor grammatical and vocabulary improvements needed to bring the English up to standard.

Response: Thank you for the opportunity to revise our manuscript. We have asked one of our co-authors to thoroughly review and improve the writing to ensure greater clarity in English. We hope that the new revision meets this standard.