Oseltamivir storage, distribution and dispensing following the 2009 H1N1 influenza outbreak in Mexico

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Problem During an influenza outbreak or pandemic, timely access to antivirals is essential to reduce disease severity and transmission. Best practices in antiviral procurement, storage, distribution, prescription and dispensing must be followed for prompt drug delivery.
Approach Mexico implemented a national pandemic preparedness plan in 2006 and created a strategic antiviral stockpile. Oseltamivir powder was stored centrally in bulk for distribution to all 31 states and the capital district during an influenza outbreak.
Local setting San Luis Potosí, in northern Mexico, was one of the states most intensely affected by the 2009 H1N1 influenza outbreak.
Relevant changes The oseltamivir powder was meant to be reconstituted locally but had to be reconstituted centrally during the 2009 influenza outbreak. Doubts arose surrounding the shelf-life of the reconstituted product. As a result of these problems, the first supply of the drug reached San Luis Potosí 11 days after the influenza outbreak had begun. Furthermore, dispensing criteria at the state level had to be changed in conformity with the availability of oseltamivir.
Lessons learnt Antiviral demand forecasts should be based on clearly defined distribution and dispensing criteria and decentralization of some of the medication stockpile should be considered. Mexico's national pandemic preparedness plan needs to be updated in accordance with the lessons learnt in 2009 to improve strategic stockpile management and ensure rapid delivery of oseltamivir to the population.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Background

In 2009, Mexico was the first country in the world to declare the outbreak of a novel H1N1 human influenza virus, and San Luis Potosí was one of the Mexican states with the largest number of influenza cases.[1–3] The World Health Organization (WHO) and its Regional Office for the Americas, the Pan American Health Organization (PAHO), have pointed out that a strategic stockpile of antivirals needs to be kept on hand and ready for rapid distribution to reduce mortality and serious morbidity.[4] To achieve timely access to antiviral medication during an outbreak, best practices in drug procurement, storage, distribution, prescription and dispensing need to be followed.[5,6]

Mexico developed a national pandemic preparedness plan for influenza in 2006 and created a strategic stockpile of antiviral medication. San Luis Potosí, one of Mexico's 31 states, is located in the north of the country and has 58 municipalities. It ranks seventh lowest among the 31 states and capital district in deprivation index, its population of about 2.5 million being largely rural and, on average, of low-medium socioeconomic level.[7] Antivirals are not generally available locally for use in the public sector primary care services, but access to a national stockpile was recommended as part of pandemic planning.

This study was conducted to describe the structures, policies and processes involved in procuring, storing, distributing and dispensing antivirals during the influenza outbreak that occurred in Mexico before WHO's declaration of a pandemic, as well as to draw on lessons learnt during the 2009 H1N1 pandemic to inform future pandemic planning and ensure timely access to antiviral medication in future outbreaks.

We conducted an independent, retrospective analysis of the distribution of antiviral medication from the federal to the state level and within the state of San Luis Potosí, and we assessed the extent to which international and national recommendations were followed. In 2010, approximately 18 months after the influenza outbreak, we interviewed drug stockpile managers of the health ministries in Mexico City and San Luis Potosí and other key informants (15 people in total) to gather information about how the national pandemic preparedness plan for influenza was implemented during the month immediately following the 2009 H1N1 outbreak. We identified several key informants on the basis of their role during the outbreak and obtained from them the names of other key informants through a "snowball" approach. All key informants were individuals who actively helped to implement the national pandemic preparedness plan during the April 2009 influenza outbreak at the federal or state level. The study was approved by the Research Ethics Committee of Mexico's National Institute of Public Health.

Procurement, storage, distribution and dispensing

Strategic stockpile

In 2006 Mexico's Ministry of Health decided to create a strategic stockpile of antiviral medication in a central warehouse in Mexico City. The Ministry purchased 1 381 333 treatment courses (i.e. enough for 1.28% of the national population) of oseltamivir from the manufacturer, Roche, and opted for powder in bulk for reconstitution into oral suspension because it was cheaper, had a longer shelf-life (up to 10 years) and occupied less storage space than capsules. Each dose of oseltamivir contains 75 mg and the full treatment course consists of 10 doses (one dose twice daily for 5 days).

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A few days after the outbreak of H1N1 was announced on 17 April 2009, Roche, WHO and the governments of France and the United States of America supplemented Mexico's antiviral stockpile by donating 700 200 treatment courses of oseltamivir (Tamiflu®), which were delivered over the ensuing weeks. In addition, the Ministry of Health purchased 910 000 treatment courses of oseltamivir (Tamiflu®) and 100 000 treatment courses of Relenza® (zanamivir). These donations and purchases consisted of pre-packaged product rather than bulk powder.

Reconstitution of bulk powder

Since Mexico's entire stockpile of oseltamivir was in the form of powder in bulk, the national pandemic preparedness plan provided for using the 31 state-level public health laboratories to reconstitute the powder. However, after the outbreak the Ministry of Health realized that these laboratories were not equipped or authorized to prepare pharmaceuticals. The search for a place where the oseltamivir could be reconstituted delayed stock distribution to the states. Finally, health officials decided to use the central health ministry's only laboratory, which had a reconstitution capacity of only 5000 treatment courses daily and this further delayed distribution to the states. Additionally, the steps of the reconstitution process were unclear and had to be developed ad hoc, before distribution scale-up. Finally, doubts surrounding the product's shelf-life arose. Although the commercially available pre-packaged oral suspension of Tamiflu® – i.e. the same product obtained when the powder is reconstituted – has a shelf-life of only 10 days, the oseltamivir reconstituted from bulk during the outbreak was labelled as having a shelf-life of 6 weeks if refrigerated at 4 °C. This confused some health professionals and managers and led them to question the accuracy and trustworthiness of the information provided.

Distribution of oseltamivir

It took 11days after the national outbreak alert and 30 days after the first cases of influenza-like illness were reported in San Luis Potosí for the state's central warehouse to receive the first batch of oseltamivir suspension from the central laboratory. Over the following three weeks, 16 497 treatment courses (11 817 as capsules and 4900 as oral suspension made from reconstituting oseltamivir phosphate in bulk in the central laboratory), enough for 0.6% of the state's 2009 population, were recorded in total. Within San Luis Potosí, oseltamivir suspension and capsules were distributed from the central warehouse to the warehouse of each jurisdiction at the state capital and from there to private, social security and public hospitals, or to the only two primary care clinics (of a total of 21 local clinics) that were authorized to dispense oseltamivir.

No prioritization criteria for distribution were specified under the national pandemic preparedness plan (Table 1). An ad hoc decision by the federal Ministry of Health was made to prioritize treatment for patients hospitalized at the National Institute of Respiratory Diseases in Mexico City and prophylaxis for health-care professionals in contact with patient care. Some key informants also indicated that 120 treatment courses of oseltamivir were delivered to each state's health ministry and that the first available treatment courses were for members of the National Congress, the army and privileged families. It was only after these groups had received a sufficient drug supply that oseltamivir was made available to the population requiring antiviral treatment.

Prescription and dispensing

As the national pandemic preparedness plan provided no prescribing or dispensing guidance (Table 1), the health ministry in San Luis Potosí decided to have two public health centres dispense oseltamivir during the first days of the outbreak: one to patients who received prescriptions in the private sector (health ministry dispensing outlet) and the other to patients diagnosed at a state referral centre (Anahuac Health Centre) for the ambulatory care of patients with influenza-like illness.

During the first weeks of the outbreak the health ministry in San Luis Potosí changed its criteria for oseltamivir treatment to accord with the number of treatment courses available at the state level. At first, only patients with a risk factor for developing complications received prescriptions for oseltamivir, but it was subsequently decided that all patients with influenza-like illness or exposed to the virus should receive a treatment course and post-exposure prophylactic treatment, respectively. Moreover, many health-care professionals received treatment or post-exposure prophylaxis when oseltamivir arrived in San Luis Potosí.

Evaluation and lessons learnt

Mexico's experience is a source of important lessons for other countries, particularly middle-income countries that maintain a strategic stockpile of antiviral drugs (Box 1). First, international organizations have yet to issue specific recommendations with respect to the preferred presentation for oseltamivir stockpiles (whether bulk powder or capsules). Balicer et al. argue that bulk powder has a much longer shelf-life (up to 10 years) and costs much less than either capsules or powder in individual containers for reconstitution by the patient or client.[8] However, the costs of the equipment, suspending agent and human resources needed for reconstitution need to be taken into account when choosing between bulk powder or a pre-packaged product for individual administration. During the 2009 influenza outbreak in Mexico, a strategic stockpile consisting entirely of oseltamivir in bulk for reconstitution delayed stock distribution for more than 10 days. Hence, strategic stockpiles of oseltamivir should preferably consist of a mix of bulk powder, capsules and oral suspension. The addition of other antivirals to the stockpile should also be considered for the treatment of patients with resistance to antivirals or drug allergy.

Second, a portion of the strategic stockpile should be decentralized at the state level for rapid distribution as soon as an outbreak begins. The supply of the drug could be replenished as necessary from a large central depot. In 2007, after a simulation of an influenza outbreak, Mexico's Ministry of Health recommended decentralizing the strategic stockpile to each state to provide a more rapid response to a possible outbreak.[9] However, the recommendation was never followed or incorporated into the national pandemic preparedness plan for influenza.[10]

Third, there is a need to define quantity and dispensing criteria to improve strategic stockpile management. Mexico's strategic stockpile (enough to cover 1.28% of the national population) is smaller than the stockpiles of many other upper-middle-income countries,

Table 1. **Compliance with the national pandemic preparedness plan for influenza in Mexico between April and May 2009, according to key informants interviewed**

Antiviral stockpile supply stage	Information provided or not provided	Compliance/non-compliance during first month of the influenza outbreak	Positive implications of compliance/ non-compliance	Negative implications of compliance/ non-compliance
Purchase and storage	No information on the type of preparation to be purchased	Stockpiled oseltamivir only as bulk	Compared with capsules, bulk powder is cheaper, requires less storage space and has a longer shelf-life while not reconstituted	Lack of required infrastructure and financial and human resources during outbreak
	No information on the quantities of antivirals needed	Oseltamivir in bulk covered 1.28% of Mexico's population. Criteria for quantity purchased unknown to key informants	Less expense if population coverage low	Uncertainty about priority groups requiring antivirals first
	Recommended purchasing a mix of antiviral drugs	Contrary to the national pandemic preparedness plan, only one antiviral (oseltamivir phosphate in bulk) was purchased for stockpile.	Less expense than if two or more alternative drugs are stored	No alternative treatment available for cases with resistance to oseltamivir
	Recommended decentralized storage	Contrary to the national pandemic preparedness plan, the strategic stockpile was only centrally stored	Less expense if stockpile centrally stored	11-day delay in drug distribution during outbreak
Distribution from the central level to the states	Recommended delivery of the bulk product to each state	Contrary to the national pandemic preparedness plan, bulk powder was not delivered to the states	Central control over the production of oral suspension from bulk powder	Loss of vital time in distributing strategic stockpile
	Reconstitution of bulk powder not explained	An appropriate site for reconstituting the bulk powder had to be found and the reconstitution process had to be developed	Support from Roche and the National Medicines Regulatory Authority in developing the reconstitution process	Loss of vital time in distributing strategic stockpile
	Distribution criteria not defined	Priority given to health-care professionals, military personnel, patients hospitalized at the National Reference Centre for Respiratory Diseases and members of the National Congress and Ministry of Health	No public outcry over distribution criteria	No clear prioritization criteria and ad hoc decisions without prior stakeholder agreement
Distribution within San Luis Potosí	Not described	The Ministry of Health designed the distribution ad hoc during the first 4 weeks of the outbreak. Two outlets at the primary care level dispensed oseltamivir to anyone with a medical prescription	No need for coordination with the private sector, which was perceived as difficult by key informants	Complete reliance on the public sector and delays in distribution in this sector affected both private and public sector patients
Prescription within San Luis Potosí	Not described	The health ministry in San Luis Potosí designed its own guidelines and adapted them according to the availability of antivirals	State control over the use of antivirals	Impossible to cover everyone with influenza-like illness from the start of the outbreak; prescription guidelines changed in conformity with drug availability
Dispensing within San Luis Potosí	Not described	The health ministry in San Luis Potosí decided to set up two dispensing outlets at the primary care level for patients with influenza-like illness in the public or private sector	State control over the dispensing of antivirals	Supply bottlenecks in the public sector affected both private and public sector patients

including Brazil (5%), Romania (7%), Thailand (7%) and Algeria (25%).[11,12] If Mexico should decide to cover 25% of its population with antivirals, as some high-income countries have done, it would have to invest 12.9% of its annual health expenditure, in sharp contrast to the 0.11% invested by developed countries.[13] If it should decide to cover everybody likely to fall ill during an outbreak, it would have to cover at least 12% of the population and spend 6.2% of its total health budget.[14] Otherwise, criteria should be defined a priori for priority coverage of specific population groups, and the general population should be informed of this. For instance, PAHO recommends that antivirals be

given prophylactically to health-care professionals, firefighters, police officers and people in age groups at risk, such as children and the elderly, independent of other priority groups that a country might establish.[7]

Finally, Mexico's national pandemic preparedness plan needs to be updated to incorporate the important lessons learnt from oseltamivir distribution and dispensing during the 2009 influenza outbreak. The plan has not been updated since 2006. ■

Box 1. **Summary of main lessons learnt**

- Strategic stockpiles of antiviral medication for pandemic influenza should consist of a mix of bulk powder, capsules and suspension of oseltamivir plus other antivirals to cover patients with antiviral resistance or drug allergies.
- A portion of the strategic stockpile should be kept decentralized for more rapid distribution immediately after an influenza outbreak.
- There is a need to define quantity and dispensing criteria a priori to facilitate strategic stockpile management during an influenza outbreak.

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ملخص

تخزين الأوسيلتاميفير وتوزيعه وصرفه عقب فاشية أنفلونزا H1N1 عام 2009 في المكسيك

المشكلة إتاحة المضادات الفيروسية في الوقت المناسب شرط أساسي لخفض حدة وسراية المرض أثناء فاشية الأنفلونزا أو جائحته. ويجب اتباع أفضل الممارسات في شراء المضادات الفيروسية وتخزينها وتوزيعها ووصفها وصرفها من أجل الإيصال الفوري للعقاقير.

الأسلوب نفذت المكسيك خطة وطنية في مجال التأهب لمواجهة الجائحة في 2006 وأنشأت مخزوناً احتياطياً استراتيجياً من المضادات الفيروسية. وتم تخزين مسحوق الأوسيلتاميفير مركزياً على هيئة كميات ضخمة لتوزيعه على الولايات الإحدى والثلاثين جميعها وإقليم العاصمة أثناء فاشية الأنفلونزا.

المواقع المحلية كانت ولاية سان لويس بوتوسي في شمال المكسيك واحدة من الولايات الأكثر تأثراً بفاشية أنفلونزا H1N1 عام 2009.

التغيّرات ذات الصلة كان القصد أن يتم استنشاء مسحوق الأوسيلتاميفير موضعياً، غير أنه كانت ثمة ضرورة لاستنشائه مركزياً أثناء فاشية أنفلونزا عام 2009. وأثيرت شكوك حول فترة صلاحية المنتج المستنشأ. ونتيجة لهذه المشكلات، وصلت أولى إمدادات العقار إلى سان لويس بوتوسي بعد بدء فاشية الأنفلونزا بأحد عشر يوماً. وعلاوة على ذلك، كانت ثمة ضرورة لتغيير معايير صرف العقار على مستوى الولاية بما يتفق مع إتاحة الأوسيلتاميفير.

الدروس المستفادة ينبغي أن تستند تكهنات الطلب على المضادات الفيروسية على معايير توزيع وصرف محددة بوضوح وينبغي دراسة الأخذ باللامركزية في بعض المخزون الاحتياطي من الدواء. تحتاج خطة التأهب الوطنية لمواجهة الجائحة في المكسيك إلى التحديث وفقاً للدروس المستفادة في عام 2009 بغية تحسين تدبير المخزون الاحتياطي الاستراتيجي وضمان سرعة إيصال الأوسيلتاميفير إلى السكان.

摘要

墨西哥2009 年爆发H1N1 流感疫情后的奥司他韦存储、分发和调剂

问题 在流感疫情爆发或流行期间,及时获取抗病毒药物对降低疾病的严重程度和传播非常重要。必须遵循抗病毒药物的采购、存储、分发、处方及调剂的最佳实践,确保迅速的药物交付。

方法 墨西哥在2006 年实施了全国流感大流行预案,并建立了战略性的抗病毒药物储备。奥司他韦粉末集中散装存储,以便在流感爆发期间分发到所有 31 个州和首都区。

当地状况 墨西哥北部的圣路易斯波托西州是受2009 年H1N1 流感疫情影响最严重的州之一。

相关变化 奥司他韦粉原本计划在本地重分散,但在 2009 年流感爆发期间必须集中进行重分散。重分散产品的保质期遭到质疑。由于这些问题,第一批供应的药物在流感疫情爆发后第11 天才到达圣路易斯波托西州。此外,为了与奥司他韦的来源相适应,必须改变州一级的调剂标准。

经验教训 应根据明确定义的分发和调剂标准进行抗病毒药物的需求预测,也应考虑部分药物储备的分散化。墨西哥的全国流感大流行预案需要根据2009 年的经验教训进行更新,以改善战略性储备的管理,确保迅速向人们交付奥司他韦。

Résumé

Stockage, distribution et administration de l'oseltamivir suite à l'épidémie de grippe H1N1 survenue en 2009 au Mexique

Problème Lors d'une épidémie ou pandémie de grippe, un accès en temps opportun aux antiviraux est essentiel pour atténuer la gravité et réduire la transmission de la maladie. Il convient de suivre les meilleures pratiques en matière d'approvisionnement, de stockage, de distribution, de prescription et d'administration si l'on veut assurer une délivrance du médicament la plus rapide possible.

Approche Le Mexique a mis en place en 2006 un plan national de préparation en cas de pandémie et a créé une réserve antivirale

stratégique. Un stock d'oseltamivir en poudre était centralisé pour une distribution à l'ensemble des 31 états et à la capitale en cas d'épidémie de grippe.

Environnement local San Luis Potosí, dans le nord du Mexique, figurait parmi les états les plus durement touchés par l'épidémie de grippe H1N1 de 2009.

Changements significatifs L'oseltamivir en poudre était supposé être reconstitué localement, mais il a toutefois dû l'être de manière centralisée lors de l'épidémie de grippe de 2009. Des doutes ont commencé à se poser quant à la durée de conservation du produit reconstitué. Suite à ces difficultés, San Luis Potosí n'a reçu sa première livraison du médicament que 11 jours après le début de l'épidémie de grippe. En outre, les critères de cet état en termes d'administration ont dû être modifiés selon la disponibilité de l'oseltamivir.

Leçons tirées Les prévisions relatives à la demande de médicaments antiviraux devraient se baser sur des critères de distribution et d'administration clairement définis. Il faut également envisager la décentralisation de certaines réserves de médicaments. Le plan national mexicain de préparation aux pandémies doit être révisé en fonction des leçons apprises en 2009 afin d'améliorer la gestion stratégique des stocks et de permettre la livraison d'oseltamivir à la population dans les meilleurs délais.

Резюме

Хранение, распределение и выдача препарата оселтамивир после вспышки гриппа H1N1 в Мексике в 2009 году

Проблема Во время вспышки или пандемии гриппа в снижении тяжести заболевания и ограничении его распространения важную роль играет своевременный доступ к антивирусным препаратам. Для быстрой доставки медикаментов необходимо использовать передовые методы при закупке, хранении, распределении, назначении и отпуске антивирусных препаратов.

Подход В 2006 году в Мексике был реализован национальный план по готовности к пандемиям и был создан стратегический запас антивирусных препаратов. Порошок оселтамивира в большом объеме хранился централизованно и в случае вспышки гриппа предназначался для распределения по всем 31 штатам и столичному округу.

Местные условия Штат Сан-Луис-Потоси, расположенный в северной части Мексики, был одним из штатов, которые в наибольшей степени пострадали от вспышки гриппа H1N1 в 2009 году.

Осуществленные перемены Запас порошка оселтамивира должен был быть приготовлен к использованию на местных уровнях, но во время вспышки гриппа в 2009 году его пришлось подготавливать к использованию централизованно. Возникли вопросы по поводу сроков хранения подготовленного к использованию продукта. В результате этих проблем первые поставки медицинского препарата достигли штата Сан-Луис-Потоси через 11 дней после начала вспышки гриппа. Более того, критерии отпуска на уровне штата пришлось изменить, чтобы привести их в соответствие с наличием оселтамивира.

Выводы Прогнозирование потребности в антивирусных препаратах должно основываться на четко определенных критериях распределения и выдачи, также необходимо рассмотреть целесообразность децентрализации некоторых медицинских складов. Национальный план Мексики по готовности к пандемиям необходимо откорректировать в соответствии с уроками, полученными в 2009 году, чтобы улучшить стратегическое управление запасами и обеспечить быструю доставку оселтамивира населению.

Resumen

Almacenamiento, distribución y dispensación de oseltamivir tras el brote de gripe H1N1 en México en 2009

Situación Durante un brote o pandemia de gripe, el acceso a tiempo a antivíricos es esencial para reducir la severidad y la transmisión de la enfermedad. Han de seguirse las mejores prácticas en el aprovisionamiento, almacenamiento, distribución, prescripción y dispensación para proporcionar a tiempo los medicamentos.

Enfoque México implementó un plan de preparación ante la pandemia en 2006 y creó unas reservas estratégicas de antivíricos.l Oseltamivir en polvo fue almacenado en bruto de forma centralizada para su distribución a los 31 estados y el distrito de la capital durante un brote de gripe.

Marco regional San Luis Potosí, en el norte de México, fue uno de los estados más intensamente afectados por el brote de gripe H1N1 de 2009.

Cambios importantes Se esperaba que oseltamivir en polvo fuese reconstituido localmente, pero tuvo que ser reconstituido de forma centralizada durante el brote de gripe de 2009. Aparecieron dudas sobre la vida útil del producto reconstituido. Como resultado de estos problemas, el primer suministro de medicamento llegó a San Luis Potosí 11 días después del comienzo del brote de gripe. Además, a nivel estatal los criterios de dispensación tuvieron que cambiarse de acuerdo con la disponibilidad de oseltamivir.

Lecciones aprendidas Las predicciones de demanda antiviral han de estar basadas en criterios claramente definidos de distribución y dispensación, y ha de tenerse en cuenta la descentralización de parte de las existencias del medicamento. El plan nacional de preparación ante la pandemia de México ha de ser actualizado de acuerdo con las lecciones aprendidas en 2009 para mejorar la gestión estratégica de existencias y asegurar la rápida provisión de oseltamivir a la población.

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